The Egyptian Rheumatologist xxx (xxxx) xxx

Contents lists available at ScienceDirect

The Egyptian Rheumatologist

journal homepage: www.elsevier.com/locate/ejr

Is leptin receptor gene (Gln223Arg) polymorphism associated with disease susceptibility and severity in patients of primary knee osteoarthritis?

Samia M. Fadda [a], Enas A. Abdelaleem [b], Rabab A. Mohamed [c], Hanaa M.H. Mansour [b], Noha A. Doudar [c,*]

[a] Rheumatology and Rehabilitation Department, Faculty of Medicine, Cairo University, Cairo, Egypt
[b] Rheumatology and Rehabilitation Department, Faculty of Medicine, Beni-Suef University, Beni-Suef, Egypt
[c] Clinical and Chemical Pathology Department, Faculty of Medicine, Beni-Suef University, Beni-Suef, Egypt

ARTICLE INFO

Article history:
Received 13 April 2019
Accepted 22 April 2019
Available online xxxx

Keywords:
Body mass index
Knee osteoarthritis
Kellgren-Laurence grading
Leptin
Polymorphism

ABSTRACT

Aim of the work: A significant role of Leptin receptor (LEPR) is documented in inflammation, body weight homeostasis and maintenance of cartilage. This study was conducted to detect the existence of genetic association between Knee osteoarthritis (KOA) susceptibility and severity; and LEPR (Gln223Arg) single nucleotide polymorphism (SNP).

Patients and methods: 73 primary KOA patients and 73 matched healthy controls were studied. Kellgren Laurence (K/L) radiographic grading system, Western Ontario and McMaster Universities Arthritis Index (WOMAC) score and Visual Analogue Scale (VAS) were used to assess the severity of KOA. LEPR Gln223Arg SNP (rs1137101) was genotyped in KOA patients and controls using polymerase chain reaction-restriction fragment length polymorphism (PCR –RFLP) technique and verified by direct DNA sequencing.

Results: In the current study, a significant genetic association was found between KOA patients carrying the AA genotype of LEPR and the extent of radiological severity ($p < 0.044$). In addition, a significant difference was detected within the patients between Body Mass Index (BMI) and the SNP. Patients carrying the wild type (GG) genotype showed lower body mass index (BMI) in comparison to patients carrying the heterozygous (AG) genotype and the mutant (AA) genotype ($p < 0.032$). However, no direct genetic association was detected between the SNP and KOA.

Conclusion: Leptin receptor gene (Gln223Arg) SNP might be associated with severity of KOA. There is a significant genetic association between the SNP and BMI hence, LEPR SNP might be indirectly associated with the incidence of KOA. Furthermore, the SNP is not directly associated with KOA susceptibility in the Egyptian population.

1. Introduction

Although the etiology of osteoarthritis (OA) is incompletely understood, mechanical trauma and altered genetics are involved in the pathogenesis of OA, also the immune system and proinflammatory cytokines might play a role as helper T cells (CD4+) were detected in OA synovium and its level was similar to that of rheumatoid arthritis (RA) [1]. Obesity is a relevant risk factor for OA [2], principally in knees as a weight-bearing joints [3], nevertheless, the fact that patients with overweight are also at an increased risk of OA of wrists or hands (that are non-weight bearing joints), reveals that white adipose tissue (WAT) secretes soluble factors, such as leptin that may play a role [4]. Knee osteoarthritis (KOA) is a common problem in Egypt and several studies have been conducted on Egyptian patients in order to study the effect of the disease on functional and radiological findings [5] and to determine potential biomarkers such as midkine [6], cartilage oligomeric matrix protein [7], vascular endothelial growth factor [8] or micro RNA-146a expression [9].

Leptin is a non-glycosylated protein, produced principally by adipocytes and its levels positively correlate with WAT mass under physiological conditions [4]. In 2 previous studies on Egyptian patients, the role of leptin has been investigated and a notable effect on the functional status in KOA has been revealed [10,11]. It performs its biological functions by binding to leptin receptor

Peer review under responsibility of Egyptian Society of Rheumatic Diseases.
* Corresponding author at: Clinical and Chemical Pathology Department, Faculty of Medicine, Beni-Suef University, Beni-Suef 62511, Egypt.
E-mail address: Noha_Ad@hotmail.com (N.A. Doudar).

https://doi.org/10.1016/j.ejr.2019.04.006
1110-1164/Publishing services provided by Elsevier B.V. on behalf of Egyptian Society of Rheumatic Diseases.

Please cite this article as: S. M. Fadda, E. A. Abdelaleem, R. A. Mohamed et al., Is leptin receptor gene (Gln223Arg) polymorphism associated with disease susceptibility and severity in patients of primary knee osteoarthritis?, The Egyptian Rheumatologist, https://doi.org/10.1016/j.ejr.2019.04.006

(LEPR) that is a member of class I cytokine receptor family [12]. LEPR signaling pathways are signal transducer and activator of transcription and Janus kinase [13]. A role of leptin is proposed in immune system because most immune cells express LEPR [4]. There are numerous LEPR isoforms, soluble, short and long capable of transducing signals of leptin; the long form is expressed in almost all tissues, including human articular chondrocytes [4]. Leptin and LEPR pathways can changes the differentiation destiny of chondrogenic progenitors, increase their osteogenic transformation and induce arrest in cell cycle [14]. Moreover expression levels of leptin and LEPR in synovial fluid and cartilage from joints with severe OA were found to be significantly higher [15]. An association between leptin gene SNPs and KOA susceptibility [16] and between LEPR SNPs and obesity have been suggested as risk factors for OA [17].

Impairment of leptin signaling pathway was linked to the pathogenesis of OA [18] and due to the pivotal role of LEPR in the regulation of leptin activity, direct association with the susceptibility of KOA has been suggested [19]. The association of LEPR SNPs and primary KOA in Egyptians remains unknown and has thus been considered for investigation. The associations with the severity to KOA represented by Kellgren-Laurence (K/L), Western Ontario and McMaster Universities Arthritis Index (WOMAC) and visual analogue scale (VAS) were also assessed. The relation with the body mass index (BMI) was also well thought-out.

2. Patients and methods

Seventy-three Egyptian patients (58 females and 15 males) suffering from primary KOA diagnosed according to the American College of Rheumatology (ACR) classification [20] and 73 age and sex matched healthy control subjects (61 females and 12 males) were enrolled in the present case-control study. Patients with primary KOA were enrolled from the outpatients' clinic of Rheumatology and Rehabilitation department in Beni-Suef University Hospital, between January 2017 and June 2017. Patients with Knee trauma, surgery, secondary osteoarthritis, or rheumatic diseases were excluded from the study. Healthy controls were unrelated Egyptian individuals subjects living in the same geographical region, and had no symptoms or signs suggesting OA; also they had normal radiological assessment of both knees. The study was approved by the ethical committee of BeniSuef University in accordance with the declaration of Helsinki ethical standards (FMBSUREC/06012019/Hassan).Informed consent was obtained from all participants in the study.

All participants were subjected to full history taking, complete clinical examination as well as radiological examination of both knees and the body mass index (BMI) was calculated. Patients and controls were subjected to measurement of serum concentrations of total cholesterol, triacylglycerol (TAG), high and low density lipoproteins (HDL-C and LDL-C) using automated enzymatic analyses (Beckman Coulter, AU480, USA), after overnight fasting (from 8 to12 hours) except for water. None was on lipid lowering medication, oral estrogens, glucocorticoids or alcohol intake.

Radiographic K/L grading system was used to classify KOA severity into: mild (K/L grade 2), moderate (K/L grade 3) and severe (K/L grade 4) [21]. WOMAC score was used to assess the severity of symptoms of KOA [22]. The patients were stratified according to VAS [23] into 2 groups of pain intensity: VAS score ≤ 6 and VAS Score > 6.

2.1. Genotyping

Two ml of venous blood was withdrawn by a sterile venipuncture into a sterile EDTA vacutainer. Genomic DNA was extracted from whole blood using GF-1 DNA Mini Kit (Vivantis technologies Sdn. Bhd.; Selangor, Malaysia), according to the manufacturer protocol. Polymerase chain reaction-restriction fragment length polymorphism (PCR –RFLP) technique was carried out for amplifying and detecting the genotypes of Gln223Arg polymorphism inLEPR (rs1137101). Sequence of primers5′-TCCTGCTTTAAAAGCCTAATC CAGTATTT-3′ (forward) and 5′-AGCTAGCAAATATTTTTGTAAG CAAT-3′ (reverse) were used for amplification (Invitrogen, Thermo Fisher Scientific, USA). A total PCR reaction mixture of 25 μL consisted of 4 μL purified DNA template, 2 μL of forward and reverse primers, 12.5 μL Reaction Mix and 6.25 μL ddH2O. PCR was performed under the following cycling conditions: DNA was denaturated for 4 min at 95 °C then 30 cycles of 30 s at 94 °C , the annealing step operated at 59.5 °C then 72 °C each for 30 s, at last a final extension step for 7 min at 72 °C. Overnight digestion of amplified DNA with MspI restriction enzyme (Thermo Fisher Scientific, USA) was done according to the manufacturer protocol. The digested DNA products were separated on agarose gel, stained by ethidium bromide and visualized by ultraviolet light. The digested products yielded a 367 bp fragment which represents GG genotype, 242 bp and 125 bp fragments represents AA genotype, and 367, 242 and 125 bp represents AG genotype (Fig. 1). The accuracy of RFLP results was tested using direct DNA sequencing of 30% of cases and controls with Applied Biosystems® 3500 Genetic Analyzers (Thermo Fisher Scientific, USA). The results were 100% concordant.

2.2. Statistical analysis

It was performed using SPSS software (statistical package of social science; SPSS Inc., Chicago, IL, USA) version 16. Mean ± SD, median and range, were calculated for quantitative data, while qualitative data was measured by frequency. Mann Whitney U and Kruskal Wallis tests were done to determine the significance in the difference between 2 and >2 non-parametric variables respectively. Chi-square-test (χ^2) was used to compare qualitative data while Fisher's exact test was used when the count of cell was <5, Odds ratios (ORs) with 95% confidence intervals (CI) were calculated to test association between Gln223Arg polymorphism and KOA risk. Spearman's correlation test and multiple linear regression were calculated. The Chi-square test was used to calculate the Hardy-Weinberg equilibrium for genotypes and alleles in the study and control groups. The level of significance was considered at p- <0.05.

3. Results

In the present study, the mean age of patients was 56.6 ± 8.2 years and they were 58 females and 15 males. The age (53.2 ± 9.01 years) and gender (61 females and 12 males) of the control was comparable (p = 0.09 and p = 0.52 respectively). The BMI was significantly higher in patients (33.4 ± 5.7; 22.7–46.6) compared to control (29.3 ± 3.9; p < 0.0001). 49.3%ofpatients had a positive family history of OA. The demographic features, clinical characteristics and radiographic severity of the patients are presented in Table 1.There was a significant difference in triglycerides level between patients and control (185.9 ± 15.7 and 86.6 ± 12.5 mg/dL respectively) (p < 0.001) (Table 1).

The frequency distribution of LEPR (Gln223Arg) variants in both the study and control groups conformed to Hardy–Weinberg equilibrium (p = 0.144 and p = 0.34, respectively). No significant difference was found between patients and control regarding the genotype and allele frequency distribution of LEPR (Gln223Arg) SNP (Table 2). The GG, AG and AA genotypes were comparable

Please cite this article as: S. M. Fadda, E. A. Abdelaleem, R. A. Mohamed et al., Is leptin receptor gene (Gln223Arg) polymorphism associated with disease susceptibility and severity in patients of primary knee osteoarthritis?, The Egyptian Rheumatologist, https://doi.org/10.1016/j.ejr.2019.04.006

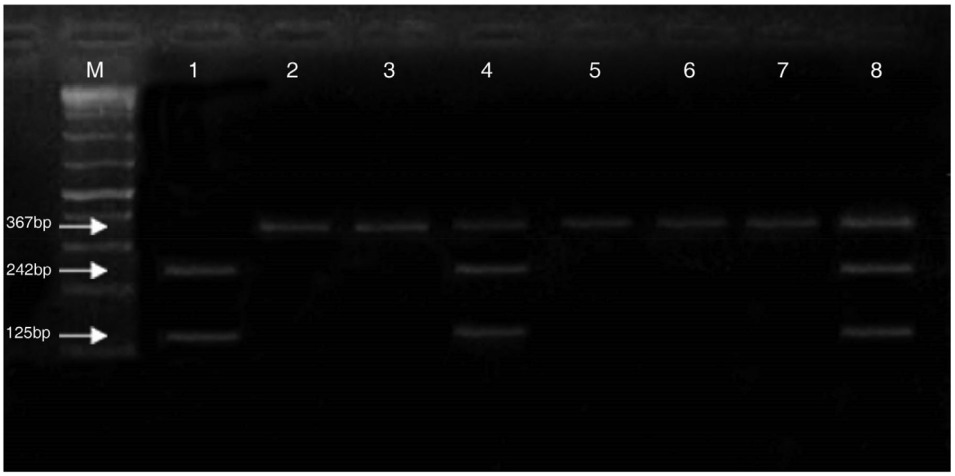

Fig. 1. Agarose gel electrophoresis of PCR –RFLP of LPER gene (Gln223Arg SNP); lane 1 shows homozygous (AA) genotype; Lanes 2,3,5,6,7 show homozygous (GG) genotype; Lanes 4 and 8 show heterozygous (AG) genotype.

Table 1
Demographic features, clinical characteristics and radiological grading in patients with primary knee osteoarthritis.

Variable mean ± SD (range) or n(%)	KOA cases (n = 73)
Age (years)	56.6 ± 8.2(41–75)
Sex (male:female)	15/58
Disease duration(years)	5.4 ± 3.6 (1–15)
Body mass index	33.4 ± 5.7
WOMAC	53.41 ± 11.5 (13–90)
VAS-pain	5.5 ± 1.2(3–10)
Cholesterol (mg/dl)	189.4 ± 66
Triglycerides (mg/dl)	185.9 ± 15.7
HDL (mg/dl)	40.3 ± 15.9
LDL (mg/dl)	123.4 ± 67
K/L grades	
Grade 2	23 (31.5)
Grade 3	34 (46.6)
Grade 4	16 (21.9)

KOA: knee osteoarthritis, WOMAC: Western Ontario and McMaster Universities Arthritis Index; VAS: visual analogue scale; HDL: high density lipoprotein, LDL: low density lipoprotein; K/L: Kellgren-Laurence.

Table 2
LEPR (rs1137101) gene polymorphism in knee osteoarthritis patients and control.

Variable n(%)	KOA patients (n = 73)	Control (n = 73)	p
Genotypes:			
GG	36 (49.3)	36 (49.3)	0.17
AG	34 (46.6)	28 (38.4)	
AA	3 (4.1)	9 (12.3)	
Alleles:			
G	106 (72.6)	100 (68.5)	0.44
A	40 (27.4)	46 (31.5)	

KOA: knee osteoarthritis.

between females (46.6%, 48.2% and 5.2%) and males (60%, 40% and 0%) patients (P = 0.499).

A significant association was present between the patients' BMI and the LEPR (Gln223Arg) SNP. Patients carrying the AG genotype had the highest BMI compared to the GG and AA (p = 0.03) (Table 3). The BMI tended to be higher in the control carrying the AA genotype compared to the GG and AG (30.4 ± 3.5, 27.9 ± 3.6 and26.7 ± 4.7, respectively). Carriers of the AA genotype had the highest K/L score (p = 0.04). There was no effect of the LEPR Gln223Arg SNP genotypes on the WOMAC or VAS (Table 3). After adjusting this association for BMI, age and disease duration on regression analysis no significant association with the K/L was detected (Table 4).

4. Discussion

Increases in life expectancy and obesity lead to rise in the prevalence of OA worldwide to be the most common form of arthritis and a principal cause of disability and pain [24]. The disease has a complex nature with many other risk factors as gender, menopausal status and previous joint trauma [25].However these risk factors do not fully explain the risk of an individual to develop OA or the progression of disease severity [26]. It is thought that genetics contribute to about 30% of the risk of OA; this molecular contribution has been previously delineated [27]. Recently impaired signals of leptin hormone have been identified as a new player in the pathophysiology of OA as it exerts its proinflammatory and pro-catabolic activities on cartilage [28]. Leptin has been known as a cytokine-like factor with pleiotropic actions that primarily enhance the production of destructive mediators. On the other hand, leptin seems to exert compensatory anabolic responses on cartilage; that is characteristic for the early development of OA [29].The importance of LEPR in regulating leptin signal pathway and the expression of LEPR within the human cartilage suggested the LEPR SNPS as possible genetic risk factor for OA. The SNP rs1137101, (Gln223Arg) within LEPR gene, represents a change in the extracellular domain of the LEPR protein, by the replacement of the amino acid glutamine with arginine at codon 223, which results in a structural change in LEPR and hence the signaling capacity of leptin might be altered [30].

In the current study, the triglycerides were significantly higher among KOA patients compared to controls. In agreement, *Gkretsi and colleagues* pointed to OA as being a metabolic disease, based on many observations such as its affection of non-weight bearing joints, deposition of lipid in the joints at the early stages of joint affection and the revealed deregulation in the expression of lipid metabolism-related genes [31].

In the present work, no direct genetic association was detected between Gln223Arg SNP and the susceptibility of primary KOA or any differences in frequency distribution of alleles or genotypes based on gender. On the contrary, two previous studies on Chinese populations indicated that LEPR SNP (Gln223Arg SNP) was associ-

Please cite this article as: S. M. Fadda, E. A. Abdelaleem, R. A. Mohamed et al., Is leptin receptor gene (Gln223Arg) polymorphism associated with disease susceptibility and severity in patients of primary knee osteoarthritis?, The Egyptian Rheumatologist, https://doi.org/10.1016/j.ejr.2019.04.006

Table 3
Association between LEPR (rs 1137101) genotypes and disease characteristics in knee osteoarthritis patients.

Variable Mean ± SD	KOA patients (n = 73)			
	GG (n = 36)	AG (n = 34)	AA (n = 3)	p
Age (years)	57.6 ± 8.5	55.7 ± 7.9	54.3 ± 5.7	0.56
Body mass index	31.6 ± 5.2	35.1 ± 5.8	34.2 ± 6.7	0.03
Disease duration (years)	5.4 ± 3.8	5.3 ± 3.4	6 ± 3.6	0.94
WOMAC	58.5 ± 20.2	58.2 ± 13.4	70 ± 7.2	0.51
VAS-pain	6.4 ± 1.5	6.3 ± 0.86	7.7 ± 0.5	0.219
K/L grading	2.3 ± 1.04	2.5 ± 0.7	3.7 ± 0.6	0.04

KOA: knee osteoarthritis, WOMAC: Western Ontario and McMaster Universities Arthritis Index; VAS: visual analogue scale; K/L: Kellgren Laurence. Bold values are significant at $p < 0.05$.

Table 4
Multiple linear regression analysis of confounding factors affecting the Kellgren Laurence score.

Independent variables	Coefficient	t	(95% CI)	P
Age	0.034	4.41	(−0.275–0.14)	**<0.001**
Body mass index	0.001	0.89	(0.019–0.05)	0.37
Disease duration	0.111	6.45	(-0.001–0.003)	**<0.001**
Genotype	−0.067	−0.65	(0.08–0.15)	0.51

Bold values are significant at $p < 0.05$.

ated with the susceptibility to KOA, and hence considered a genetic marker that may predict the risk of the disease [18,19]. This discrepancy could be attributed to differences in ethnic origins of the studied populations, the presence of other SNPs within LEPR gene associated with the susceptibility to osteoarthritis [16]; the LEPR variant might be in linkage disequilibrium with other significant alleles involved in the pathogenesis of the disease and epigenetics or other environmental risk factors as well as interactions of these factors that results in different gene expression patterns in different populations.

Radiological assessment of OA is considered the gold standard that confirms the clinical diagnosis and to evaluate the disease severity [20]. In the present study, the homozygous (AA) genotype carriers had the highest K/L scores. In disagreement, Novosleskyi et al. [32] indicated the absence of an association between the SNP in KOA patients' and different radiologic stages of the disease. Leptin participates in the regulation of the metabolism of bone [33], and contributes to abnormal function of osteoblast [34]. Impaired signaling of LEPR might result in an increase of the level of circulating serum and synovial fluid leptin thus performing its proinflammatory and procatabolic actions on cartilage [28] which might be the cause for the progression in radiologic severity in KOA patients.

Obesity is a risk factor for OA, as the knee is a weight bearing joint; hence joints of obese individuals bear more pressure than the normal population, which would lead to greater joint wear [35]. In this study, there was a significant association between the SNP and BMI, patients carrying heterozygous AG genotype have higher BMI. This was in accordance with studies on Spanish [36] and Pacific Island populations [37]. Both studies revealed that the Q223R (Gln223Arg) SNP of the LEPR gene is a risk factor for obesity. On the contrary, others reported no association [38]. These results might be attributed to the production of leptin in adipose tissue, placenta, osteoblasts and joint cartilage [39]. Further on, leptin was found to be synthesized in osteoarthrogenic joint adipose tissue and hence, obese individuals often present with high leptin levels relative to their high fat content [40]. In addition, LEPR was recently demonstrated to be naturally expressed within the native human cartilage chondrocytes, therefore impaired leptin signaling caused by the SNP together with the increased level of leptin in obese patients might explain the relation detected between patients with high BMI andGln223Arg SNPas both factors might act together to mediate the inflammatory and destructive responses of leptin in joints [18]. Moreover, it is worth noting that there is a discrepancy in BMI being obviously higher in this work compared to Yang et al. [18]. Hence, the increase in the level of bioactive leptin might overcome the effect of the receptor polymorphism in the Egyptian population.

The main limitation in this study is the small sample size which decreased the confidence in the generalizability of the results being confined to one geographical area in Egypt (BeniSuef governorate). In addition, most of the studied patients were obese. Repeating the study on a larger population of patients both obese and non-obese), with different life styles and with a longitudinal study design could be recommended to present the potential role of Gln223Arg SNP in KOA and the disease outcome among different populations. Future directions are investigating different SNPs in leptin and leptin receptor genes and to study their association with obesity and osteoarthritis as well as their relation to the medications received.

In conclusion, leptin receptor gene (Gln223Arg) SNP might be associated with radiological severity of KOA. There is a significant association between the SNP and BMI and hence, (Gln223Arg) SNP is indirectly associated with KOA. Furthermore, the SNP is not directly associated with susceptibility of KOA in the Egyptian population.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

There are no conflicts of interest.

References

[1] Nakamura H, Yoshino S, Kato T, Tsuruha J, Nishioka K. T-cell mediated inflammatory pathway in osteoarthritis. Osteoarthritis Cartilage 1999;7:401–2.
[2] Edwards C, Rogers A, Lynch S, Pylawka T, Silvis M, Chinchilli V, et al. The effects of bariatric surgery weight loss on knee pain in patients with osteoarthritis of the knee. Arthritis 2012;2012:504189.

Please cite this article as: S. M. Fadda, E. A. Abdelaleem, R. A. Mohamed et al., Is leptin receptor gene (Gln223Arg) polymorphism associated with disease susceptibility and severity in patients of primary knee osteoarthritis?, The Egyptian Rheumatologist, https://doi.org/10.1016/j.ejr.2019.04.006

[3] Wluka AE, Lombard CB, Cicuttini FM. Tackling obesity in knee osteoarthritis. Nat Rev Rheumatol 2013;9:225–35.
[4] Abella V, Scotece M, Conde J, Pino J, Gonzalez-Gay MA, Gómez-Reino JJ, et al. Leptin in the interplay of inflammation, metabolism and immune system disorders. Nat Rev Rheumatol 2017;13:100–9.
[5] Fathi HM. Unilateral versus bilateral primary knee osteoarthritis: Relation to the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC), C-reactive protein and radiological assessment in Egyptian patients. The Egyptian Rheumatologist. Epub ahead of print.
[6] Hassan WA, Mansour AI. Increased serum and synovial levels of midkine are associated with radiological progression in primary knee osteoarthritis patients. The Egyptian Rheumatologist. Epub ahead of print.
[7] Gheita TA, El-Awar AH, El-Ansary MM, Raslan HM, El-Defrawy AO. Cartilage oligomeric matrix protein (COMP) levels in serum and synovial fluid in osteoarthritis (OA) patients: correlation with clinical, radiological and laboratory parameters. Osteoarthritis Cartilage 2015;23(2):A85.
[8] El-Najjar AR, Ezzeldin N, Khalil SS, El-Gerby KM, Alazizi NM, Ibraheem HA. Vascular endothelial growth factor and colour Doppler ultasonography in knee osteoarthritis: relation to pain and physical function. Egypt Rheumatol 2018. epub ahead of print.
[9] Zakaria SS, Gaballah HH, Saadany HM. Micro RNA-146a expression, NF-kB/P65 activity and serum pentosidine levels as potential biomarkers for disease severity in primary knee osteoarthritis patients. Egypt Rheumatol 2016;38(4):319–25.
[10] Elwakil WA, Mohasseb D, Elkaffash D, Elshereef S, Elshafey M. Serum leptin and osteoporosis in postmenopausal women with primary knee osteoarthritis. Egypt Rheumatol 2016;38(3):209–15.
[11] Hussein NA, Sharara G. Correlation between serum leptin, cytokines, cartilage degradation and functional impact in obese knee osteoarthritis patients. Egypt Rheumatol 2016;38(2):117–22.
[12] Lago F, Dieguez C, Gómez-Reino J, Gualillo O. The emerging role of adipokines as mediators of inflammation and immune responses. Cytokine Growth Factor Rev 2007;18:313–25.
[13] Frühbeck G. Intracellular signalling pathways activated by leptin. Biochem J 2006;393:7–20.
[14] Zhao X, Dong Y, Zhang J, Li D, Hu G, Yao J, et al. Leptin changes differentiation fate and induces senescence in chondrogenic progenitor cells. Cell Death Dis 2016;7:e2188.
[15] Vuolteenaho K, Koskinen A, Moilanen T, Moilanen E. Leptin levels are increased and its negative regulators, SOCS-3 and sOb-R are decreased in obese patients with osteoarthritis: a link between obesity and osteoarthritis. Ann Rheum Dis 2012;71:1912–3.
[16] Qin J, Shi D, Dai J, Zhu L, Tsezou A, Jiang Q. Association of the leptin gene with knee osteoarthritis susceptibility in a Han Chinese population: a case-control study. J Hum Genet 2010;55:704–6.
[17] Quinton ND, Lee AJ, Ross RJ, Eastell R, Blakemore AI. A single nucleotide polymorphism (SNP) in the leptin receptor is associated with BMI, fat mass and leptin levels in postmenopausal Caucasian women. Hum Genet 2001;108:233–6.
[18] Yang J, Du H, Lv J, Zhang L. Association of rs1137101 polymorphism in LEPR and susceptibility to knee osteoarthritis in a Northwest Chinese Han population. BMC Musculoskelet Disord 2016;17:311.
[19] Ma XJ, Guo HH, Hao SW, Sun SX, Yang XC, Yu B, et al. Association of single nucleotide polymorphisms (SNPs) in leptin receptor gene with knee osteoarthritis in the Ningxia Hui population. Yi Chuan 2013;35:359–64.
[20] Altman R, Asch E, Bloch D, Bole G, Borenstein D, Hochenberg M, et al. Develpoment of criteria for classification of osteoarthritis of the knee and reporting of osteoarthritis; classification of osteoarthritis of the knee. Diagnostic and therapeutic criteria committee of American Rheumatism Association. Arthritis Rheum 1986;29:1039–49.
[21] Kellgren JH, Lawrence JS. Radiological assessment of osteoarthritis. Ann Rheum Dis 1957;16:494–501.
[22] Bellamy N, Buchanan WW, Goldsmith CH, Campbell JandStitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15:1833–40.
[23] Jensen MP, Karoly P, Braver S. The measurement of clinical pain intensity: a comparison of six methods. Pain 1986;27:117–26.
[24] NeogiT The. Epidemiology and impact of pain in osteoarthritis. Osteoarthritis Cartilage 2013;21:1145–53.
[25] Mabey T, Honsawek S. Genome wide association studies and next generation sequencing technologies in osteoarthritis. Next Generat Sequence Appl 2014;1:1–4.
[26] Warner SC, Valdes AM. The genetics of osteoarthritis: a review. J Funct Morphol Kinesiol 2016;1:140–53.
[27] Valdes AM, McWilliams D, Arden NK, Doherty SA, Wheeler M, Muir KR, et al. Involvement of different risk factors in clinically severe large joint osteoarthritis according to the presence of hand interphalangeal nodes. Arthritis Rheum 2010;62:2688–95.
[28] Azamar-Llamas D, Hernández-Molina G, Ramos-Ávalos B, Furuzawa-Carballeda J. Adipokine contribution to the pathogenesis of osteoarthritis. Mediat Inflamm 2017;2017:5468023.
[29] Vuolteenaho K, Koskinen A, Moilanen E. Leptin – a link between obesity and osteoarthritis. Applications for prevention and treatment. Basic Clin Pharmacol Toxicol 2014;114:103–8.
[30] Li Y, Geng J, Wang Y, Lu Q, Du Y, Wang W, et al. The role of leptin receptor gene polymorphisms in determining the susceptibility and prognosis of NSCLC in Chinese patients. J Cancer Res Clin Oncol 2012;138:311–6.
[31] Gkretsi V, Simopoulou T, Tsezou A. Lipid metabolism and osteoarthritis: lessons from atherosclerosis. Prog Lipid Res 2011;50:133–40.
[32] Novoseletskyi VO, Stanislavchuk MA, Shkarupa VM, Shvets LV. Characterization of lepr gene Q223R (RS1137101) genotypes in patients with knee joint osteoarthritis of different radiographic stages. WiadLek 2018;71:188–92.
[33] Conde J, Scotece M, Abella V, López V, Pino J, Gualillo O, et al. Basic aspects of adipokines in bone metabolism. Clin Rev Bone Miner Metab 2015;13:11–9.
[34] Findlay DM, Atkins GJ. Osteoblast-chondrocyte interactions in osteoarthritis. Curr Osteoporos Rep 2014;12:127–34.
[35] Yan M, Zhang J, Yang H, Sun Y. The role of leptin in osteoarthritis. Medicine (Baltimore) 2018;97(14):e0257.
[36] Portoles O, Sorli JV, Frances F, Coltell O, Gonzalez JI, Saiz C, et al. Effect of genetic variation in the leptin gene promoter and the leptin receptor gene on obesity risk in a population-based case–control study in Spain. Eur J Epidemiol 2006;21:605–12.
[37] Furusawa T, Naka I, Yamauchi T, Natsuhara K, Kimura R, Nakazawa M, et al. The Q223R polymorphism in LEPR is associated with obesity in Pacific Islanders. Hum Genet 2010;127:287–94.
[38] Mergen H, Karaaslan C, Mergen M, Deniz Ozsoy E, Ozata M. LEPR, ADBR3, IRS-1 and 5-HTT genes polymorphisms do not associate with obesity. Endocr J 2007;54:89–94.
[39] Conde J, Scotece M, López V, Abella V, Hermida M, Pino J, et al. Differential expression of adipokines in infrapatellar fat pad (IPFP) and synovium of osteoarthritis patients and healthy individuals. Ann Rheum Dis 2014;73:631–3.
[40] Lonnqvist F, Arner P, Nordfors L, Schalling M. Overexpression of the obese (ob) gene in adipose-tissue of human obese subjects. Nat Med 1995;1:950–3.

Please cite this article as: S. M. Fadda, E. A. Abdelaleem, R. A. Mohamed et al., Is leptin receptor gene (Gln223Arg) polymorphism associated with disease susceptibility and severity in patients of primary knee osteoarthritis?, The Egyptian Rheumatologist, https://doi.org/10.1016/j.ejr.2019.04.006