Association of HLA-DQB1 with the development of osteoarthritis

Osteoartrit gelişimi ile HLA-DQB1'in ilişkisi

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Abstract
Osteoarthritis (OA) is a degenerative disease characterized by chronic inflammation of different joints in the body, which may lead to joint destruction and life disability. It is a complex disease of multifactorial etiology like genetic variation. Genetics is believed to be important in determining the susceptibility of OA. It was proven to be associated with histocompatibility locus antigen region. The aim of this study was to analyze of the frequencies of HLA-DQB1 alleles in OA Iraqi Arab Muslims. A cross–sectional case control comparative study included twenty six Iraqi Arab Muslims patients who had knee OA and admitted in the Orthopedic Department at Al-Kindy Teaching Hospital between September – 2012 to June – 2013, and compared to control ethnically matched group. HLA–DRQ1 genotyping was done by polymerase chain reaction-sequence-specific oligonucleotide probes (PCR-SSOP) method. There was an increased frequencies of HLA-DQB1*03:01:01 in patients with OA compared with healthy controls (P=0.0171, odds ratio=7.4118, 95% CI=1.4285-38.4564); also there were an increase in the HLA-DQB1* 02:01:01, HLA-DQB1* 0305 and *04 in patients with OA compared with the control group, but the differences were not statistically significant. Our results suggest a role of the HLA DQB1*03:01:01 system in the etiopathogenesis of OA.
Keywords: Genetic; HLA; osteoarthritis

Özet
Osteoartrit eklem hasarı ve yaşam güçsüzlüğüne yol açabilen vücudun farklı eklemlerinde kronik inflamasyon ile karakterize dejeneratif bir hastalıktır. Genetik varyasyon gibi multifaktoriyel etyolojisi olan kompleks bir hastalıktır. Genetiğin osteoartrite duyarlılığın saptanmasında önemli olduğuna inanılır. Bunun histokompatibilite lokusu antijen bölgesi ile ilişkili olduğu kanıtlanmıştır. Bu çalışmanın amacı, osteoartritli Irak'lı Arap Müslümanlarda HLA-DQB1 alleli sıklığını analiz etmekti. Çapraz kesitli vaka kontrol çalışmasına Al-Kindy Eğitim Hastanesi Ortopedi Anabilim Dalı'na Eylül 2012 – Haziran 2013 arasında başvuran ve diz osteoartriti olan 26 Irak'lı Arap Müslüman hasta dahil edildi ve etnik olarak uyan kontrol grubuyla karşılaştırıldı. HLA–DRQ1 genotiplemesi polimeraz zincir reaksiyonu-dizi spesifik oligonükleotid problar (PCR-SSOP) metodu ile yapıldı. Sağlıklı kontrollerle karşılaştırıldığında osteoartritli hastalarda HLA-DQB1*03:01:01 sıklığı artmıştı (P=0.0171, odds oranı=7.4118, 95% CI=1.4285-38.4564); aynı zamanda hastaalrda HLA-DQB1* 02:01:01, HLA-DQB1* 0305 ve *04'de artmıştı, fakat farklılık istatistiksel olarak anlamlı değildi. Sonuçlarımız, osteoartrit etyopatogenezinde HLA DQB1*03:01:01 sisteminin rolünü düşündürmektedir.
Anahtar kelimeler: Genetik; HLA; osteoartrit

Introduction

Osteoarthritis (OA) is the most frequent form of arthritis in many elderly individuals and patients complain from joint pain, swelling, tenderness and accompanied by varying degrees of functional restriction and reduced quality of life. Pain is usually in the large weight bearing joints such as the knees and hips. It also affects other joints like hand (1). OA can occur in every synovial joint of different joints like hip, knee, hand, foot and spine. The prognosis of the disease is differ according to type of joint involvement for example knee osteoarthritis is very changeable in its prognosis and about a period of several years some of them were improved and the rest developed a progressive symptomatic disease. Other joint like hip osteoarthritis probably has the most horrible overall outcome and some hips heal unexpectedly (2).

Osteoarthritis is a familial disorder caused by a mixture of genetic and environmental factors. Environmental factors include way of life factors such as being obese, inactive job, recurring use of joints and trauma to affected joints (3). The genes that predispose to osteoarthritis remain to be clarified. Many studies have pointed to different HLA class I and II associations, perhaps indicating the heterogeneity of the condition (4). Several studies on

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generalized osteoarthritis have revealed an association with HLA alleles and there is a relation between HLA-A*01 and HLA-B*08 alleles and OA (5,6). Other studies reported no any relation with HLA typing (7). Still other study reported that there was a connection between HLA-A*02 and HLA-B*38 with OA, and HLA-B*44 positivity may be associated with familial OA and HLA-A*29 may be a preventive factor against development of diseases (8).

The main aim of this study is to assess if there is any association between HLA-DQB1 and OA in Iraqi Arab Muslims and to determine the genetic effect on the development of this disease thereby potentially suggesting strategies for prevention and treatment, rather than as a diagnostic tool.

Patients and Methods

A cross–sectional case control comparative study included twenty six Iraqi Arab Muslims patients who had knee OA and admitted in the Orthopedic Department at Al-Kindy Teaching Hospital between September 2012 to June 2013. Age of the patients group was ranged from 35-70 years. Females were 24 (92.3%) and the rest were males (7.69%). The patients were selected by the orthopedician according to the clinical presentation and X-ray changes. Any patients with secondary OA were excluded from the study. The control group consisted from thirty healthy volunteers among the staff of Al-Kindy College of Medicine that did not have any OA. The control group was ethnically similar to patients group, their ages were ranged from 30-60 years. Males were 18 (60%) in number and the rest were females (40%).

The Scientific and Ethical Committee of Al-kindy medical college and Al-Kindy Teaching Hospital has been approved the study. Informed consent was obtained from all patients and control group. This study has been performed in accordance with the Declaration of Helsinki.

HLA genotyping

Peripheral venous blood samples from patients and control groups were collected in ethylenediaminetetraacetic acid-containing tubes and then stored at -20°C until testing for class II, HLA-DQB1. Genomic DNA was extracted using Promega DNA extraction kit, USA. DNA product was verified by electrophoresis in a 2% agarose gel containing ethidium bromide and was visualized under UV light. Locus- and allele-specific amplifications of genomic DNA were performed for DQB1. Amplification and hybridization was performed using a panel of sequence-specific oligonucleotide probes (SSOP) using HLA-DQB1 amplification and hybridization kits (SSO HLA type DQB1 plus and Mastermix for HLA type DQB1 Amp plus kits, Innogenetics, Belgium) using automated method by AutoLipa 48, Innogenetics, Belgium. The results were interpreted using LiRas version 5.0 software, Innogenetics, Belgium.

Statistical analysis was done using using MiniTab version 3.0 software. The distribution of HLA alleles in patients and control groups were compared using Chi-square for nominal variable. Fisher's exact test was used when necessary. In each comparison, the odds ratio (OR) along with the 95% confidence interval (95% CI) was used. P value less than 0.05 was considered statistically significant.

Results

Control and OA patients groups were typed for identifying the DQB1* alleles using DNA-based methodology (PCR-SSOP). Alleles frequencies of HLA-DQB1 for OA patients and control group is shown in Table 1. There was an increased frequencies of HLA-DQB1*03:01:01 in patients with OA compared with healthy controls (P=0.0171, odd ratio=7.4118, 95% CI: 1.4285-38.4564); also there is an increase in the HLA-DQB1* 02:01:01, HLA-DQB1* 0305 and *04 in patients with OA compared with the control group, but the differences were not statistically significant.

Discussion

Osteoarthritis is a degenerative disease of the articular cartilage. It is a multifactorial disease caused by a genetic, metabolic or mechanical factors cause an early injury to the cartilage resulting in release of several cartilage specific antigens leading

Table 1. Human leukocytes antigens (HLA-DQB1) alleles frequencies in patients with OA and healthy control groups.

HLA-DQB1* alleles	OA patients group n=26		Healthy control group n=30		Odd ratio (95% confidence interval)	P- value
	n	%	n	%		
02:01:01	17	65.38	0	0	na	na
02:02:02	0	0	5	16.66	na	na
02:04:01	0	0	5	16.66	na	na
02:05:01	0	0	4	13.33	na	na
03:01:01	9	34.61	2	6.66	7.4118 1.4285 - 38.4564	0.0171
03:05:01	8	30.76	0	0	na	na
04:01:01	9	34.61	0	0	na	na
04:01:02	9	34.61	0	0	na	na
05:01:01	0	0	8	26.66	na	na
06:01:01	0	0	6	20	na	na

na = not applicable

at the end to destruction of the cartilage. Among the genetic factors, HLA has been reported to associate with OA. In our study we found an association between OA and HLA-DQB1*03:01:01 compared with healthy controls. These data must be considered as an introduction to this association because the patient numbers tested in this study were not large enough and only involved a single race that they are Arab Muslims. Other study showed no association with HLA-DQB1 and OA in Japanese population (9), this may be due to race and religion factors. It has been found for autoimmune diseases that HLA class II associations are different for the various ethnic groups and the same apply to OA (10). Short arm of chromosome 6 (6p21.3) contains both HLA and the gene encoding the α2 chain of type XI collagen (*COL11A2*) that are tightly linked and linkage of female hip OA to *HLA*/*COL11A2* has been demonstrated (11). Other reports demonstrated that HLA-B35, B40, DQ1, and CW4 antigens were overrepresented in the OA patients and haplotype analysis showed an association of B35-DQ1, B40-DQ1, and DR2-DQ1 with increased OA risk (12).This discrepancy may be due to criteria of sample collection, in our study we select knee OA while in this study was hand OA in addition to genetic factors. It had been found that class II molecules are directly implicated in the etiology and pathogenesis of autoimmune disease. The initiation of an immune response against autoantigens requires T cell activation that requires the presence of both antigen and HLA-class II on antigen presenting cells and structural differences between class II molecules can influence this interaction between T cell and antigen either at the level of antigen presentation or during T cell differentiation in the thymus (13).The role of the various HLA alleles on OA susceptibility were unusual in different ethnic populations and it comprise the susceptibility and non-susceptibility to disease development that were also different. Therefore, studies of OA associated HLA alleles should be on the basis of region, nationality, the sample size and typing technology. This will benefit to understand the pathogenesis, early diagnosis and the prevention and control of OA.

In conclusion, our results suggest a role of the HLA DQB1*03:01:01 system in the etiopathogenesis of OA.

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