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The Role of Human Leukocyte Antigen Typing in Libyan Patients with Chronic Periodontitis

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Abstract

Background: Periodontitis is an inflammation of gums and teeth bone that caused by certain bacterial normal flora in the mouth leading to destroy periodontal tissues. Human leukocyte antigen (HLA) gene has an important role in determinant the susceptibility and progression of periodontitis in human to facilitate diagnostic and therapeutic value. This study was performed to find out the association between HLA classes I and II genes with chronic periodontitis.

Material and methods: A total of 114 individuals (60 patients with chronic periodontitis and 54 controls) were collected from Tripoli Central Hospital. All study population was examined clinically using Ramfjord chart for diagnosis the periodontitis cases and subsequently were analyzed their blood samples using specific-sequence oligonucleotide PCR (SSO-PCR) assay for typing various HLA loci.

Results: Distribution of different HLA-B and HLA-A loci among patients and control individuals were statistically significant in the HLA-B45 and HLA-A30 alleles, $P<0.03$ and $P<0.04$, respectively. Furthermore, statistically significant differences were observed between patients and controls in HLA-DRB^{1}14 and HLA-DRB5 alleles, $P<0.00$ and $P<0.00$, respectively. Generally, there is non-significant differences were observed in HLA-DRB^3, HLA-DRB^4 loci.

Conclusion: The HLA-B45 and HLA-A30 alleles may represent as risk factors for chronic periodontitis cases in Libyan population, whereas HLA-DRB^{1}14 and HLA-DRB^5 may indicate to protective factors for chronic periodontitis among Libyan populations.

Introduction

Chronic periodontal disease is a variable from simple gingival disease to aggressive and necrotizing general periodontitis [1]. The distribution of periodontal diseases among all populations were small percentage (10-15%) [2]. The study that performed by 3rd national health and nutrition examination survey (NHANES III) (1999-2004) was revealed that 8.52% of American adults between age 20 to 64 have periodontal disease [3].

Genetic factor clearly play a role in the predisposition to progression of periodontal diseases [8] in form of common genetic polymorphisms and rare mutation in the population [9]. This differential genetic expression for chronic periodontitis is associated with genetic elements of susceptibility [25-28]. Such studies were suspected that periodontitis could be polygenic (gene-gene interactions) and multifactorial (geneenvironment-life style interactions such as oral hygiene, smoking, stress and diet) [29, 30]. Further published studies discussed the HLA association with different ethnic origin and chronic periodontitis [10,24]. There are different genes encoding the HLAs that consider candidate markers for periodontitis because of involved in regulating immune responses [11]. The association between HLA genes and the susceptibility to severe chronic periodontitis (CP) was showed in the allele frequencies of DRB^1*1501, which was more frequently in severe CP patients than in controls [11]. Reichert et al. indicated that HLA-B*15 was a significant risk factor for generalized aggressive disease and was positively correlated with the disease severity and may have a potential use in the future management of generalized aggressive periodontitis [12]. In addition, other study showed that female acute periodontitis (AP) patients have an increase in the frequency of HLA-A*68/69 and a decrease in the frequency of DRB blank* (nonDRB3/4/5*) and DQB^1*05 positive probands [12]. Therefore, certain HLA alleles seem to be associated with susceptibility or resistance to periodontitis patients as published in previous studies [11,12,13]. The current study going to investigate genes markers human leukocyte antigens (HLAs) class I and II genotypes as risk factor that associated with chronic periodontitis in a group of Libyan patients.

Further studies were revealed that periodontitis was dominant and associated with different parameters such as male gender, Mexican race, low education, current smokers, diabetes, stress, crooked or crowded teeth, medications that cause dry mouth, immune-deficiencies, hormonal changes in women [4-9].

Additional study was determined the susceptibility of people to extra destructive process by using genetic and immunological response, which was evaluated as 10-15% and recurrent among members of the same family [10].

Material and Methods

Patient selection

The study was conducted at Tripoli Central Hospital. Patient and control subjects coming for routine follow up and were asked to participate in the research. Total subjects participated in the study were 114 (60 patients with chronic periodontitis and 54 controls without chronic periodontitis).

Clinical risk scores of periodontal disease

Diagnosis of periodontal disease was performed by detection of any pathological condition that affecting tooth supporting structures. Each patient was checked clinically by using of case history analysis recording, an evaluation of clinical examination, various diagnostic aids such as radiographs and laboratory investigations.

All patients were examined using measurement of probing depth, clinical attachment loss, bone resorption, and tooth mobility. In addition, scoring method of periodontal disease index (PDI) of Ramfjord for diagnosis of periodontitis was achieved.

Laboratory diagnosis

DNA extraction: Peripheral whole blood (5 ml) with anti-coagulant (EDTA) tube was collected from each of individual. DNA extraction of blood samples were performed under standardized techniques of Dynabeads® DNA DIRECT™.

Sequence-specific oligonucleotide PCR (SSO-PCR) assay: Sequences HLA-genes were detected by using specific-sequence-oligonuclutide (SSO-PCR) assay, which based on three major processes; PCR target amplification, hybridization of the amplified products to an array of immobilized SSO probes, and detection of the probe-bound amplified product.

Statistical analysis: All collected data were analyzed by using SPSS programs, which showed the relationships between HLA class I (HLA-A and HLA-B) genes and HLA class II (DRB^1, DRB^3, DRB^4, DRB^5) genes among patients and controls.

Values of $P<0.05$ were considered statistically significant while P values of ≥ 0.05 were considered not significant. Statistical analysis was based on chi-squared testing and P-values of small size samples were corrected by Fisher's exact test.

Results

Demographic data of periodontitis cases

As shown in Table 1, the majority of chronic periodontitis cases were obtained in males and white race. The chronic periodontitis cases were classified into four age groups as shown in Table1. The predominant prevalence was showed in age group 30-40 years while the lowest prevalence was among age group 41-51years.

Demographic data of periodontitis patients		No. of cases (%)
Gender	Male	38 (63.3)
	Female	22 (36.7)
Race	White	51 (85)
	Black	9 (15)
Age group	19-29 yrs	13 (21.7)
	30-40 yrs	26 (43.3)
	41-51 yrs	9 (15)
	52-62 yrs	12 (20)
Blood group	A+	17 (28.3)
	A-	5 (8.3)
	O+	26 (43.3)
	O-	2 (3.3)
	B+	10 (16.7)

Table 1: Proportion of periodontitis case among various parameters.

Distribution of HLA-A alleles

HLA-A alleles distribution among patients and controls individuals were showed non-significant difference in HLA-A loci, with exception, HLA-A30 was statistically significant. Table 2 showed the HLA-A2, HLA-A30 and HLA-A24 alleles are the most frequent alleles from both patients and controls by 34.2%, 22.8% and 17.5%, respectively.

The almost similar proportions of alleles scattering for HLA-A3, HLA-A24 and HLA-A68 were about (16.7%). Several HLA-A alleles (HLA-A74, 66, 35, 42 and 27) were identified only in control group while HLA-A34 allele was recorded in patients alone (Table 2).

HLA-A alleles	Total No. (%)	HLA-A allele patient No. (%)	HLA-A allele control No. (%)	P-value
A2	39 (34.2)	20 (33.3)	19 (35.2)	0.57
A30	26 (22.8)	18 (30)	8 (14.8)	0.04
A24	20 (17.5)	10 (16.7)	10 (18.5)	0.49
A3	18 (15.8)	10 (16.7)	8 (14.8)	0.49
A68	17 (14.9)	10 (16.7)	7 (12.9)	0.2
A1	13 (11.4)	6 (10)	7 (13)	0.3
A23	12 (10.5)	8 (13.3)	4 (7.4)	0.16
A29	11 (9.6)	5 (8.3)	6 (11.1)	0.42
A31	10 (8.8)	6 (10)	4 (7.4)	0.44
A33	6 (5.3)	5 (8.3)	1 (1.9)	0.12
A26	5 (4.4)	2 (3.3)	3 (5.6)	0.45
A11	5 (4.4)	1 (1.7)	4 (7.4)	0.14
A32	4 (3.5)	3 (5)	1 (1.9)	0.35
A69	2 (1.8)	1 (1.7)	1(1.9)	0.72
A34	2 (1.8)	2 (3.3)	0	0.52
A36	2 (1.8)	1 (1.7)	1 (1.9)	0.72
A74	1 (0.9)	0	1 (1.9)	0.47

A66	1 (0.9)	0	1 (1.9)	0.47
A35	1 (0.9)	0	1 (1.9)	0.47
A42	1 (0.9)	0	1 (1.9)	0.47
A27	1 (0.9)	0	1 (1.9)	0.47

Table 2: Distribution of HLA-A alleles among chronic periodontitis patients and control individuals.

Distribution of HLA-B alleles

The prevalence of HLA-B loci among total population of study were showed significant variations. The highest frequent allele was HLA-B35 (25%) in both control and patients, followed by HLA-B50 and 51 alleles circulated in higher frequency in both samples of study. The HLA-B45 allele showed significant difference (P=0.03) was only identified in patients with chronic periodontitis. While the alleles HLA-B55 and 56 were recorded only in control samples (P=0.2) (Table 3).

The frequency of periodontitis cases between different blood groups were listed in Table1. The highest percentage was demonstrated in O+ blood group followed by A+ blood group while the lowest percentage were found in O- blood group.

HLA-B allele	Total No. (%)	HLA-B allele patient No. (%)	HLA-B allele control No. (%)	P- value
B35	28 (24.6)	14 (23.3)	14 (25.9)	0.45
B50	24 (21.1)	15 (25)	9 (16.7)	0.09
B51	24 (21.1)	10 (16.7)	14 (25.9)	0.16
B15	17 (14.9)	9 (15)	8 (14.8)	0.59
B8	15 (13.2)	6 (10)	9 (16.7)	0.22
B41	14 (12.3)	7 (11.7)	7 (13)	0.52
B44	12 (10.5)	4 (6.7)	8 (14.8)	0.13
B49	11 (9.7)	5 (8.3)	6 (11.1)	0.42
B53	11 (9.6)	6 (10)	5 (9.3)	0.57
B7	11(9.6)	8 (13.3)	3 (5.6)	0.13
B78	10 (8.8)	5 (8.3)	5 (9.3)	0.56
B18	9 (7.9)	7 (11.7)	2 (3.7)	0.1
B57	6 (5.3)	4 (6.7)	2 (3.7)	0.39
B45	5 (4.4)	5 (8.3)	0	0.03
B42	5 (4.4)	4 (6.7)	1 (1.9)	0.21
B13	5 (4.4)	1 (1.7)	4 (7.4)	0.15
B52	5 (4.4)	1 (1.7)	4 (7.4)	0.15
B39	5 (4.4)	1 (1.7)	4 (7.4)	0.15
B14	4 (3.5)	4 (6.7)	0	0.07
B38	4 (3.5)	1 (1.7)	3 (5.6)	0.27
B27	4 (3.5)	2 (3.3)	2 (3.7)	0.65
B40	3 (2.6)	2 (3.3)	1 (1.9)	0.54
B58	3 (2.6)	1 (1.7)	2 (3.7)	0.46
B80	1 (0.9)	1 (1.7)	0	0.52
B56	1 (0.9)	0	1 (1.9)	0.47

B55	1 (0.9)	0	1 (1.9)	0.47

Table 3: Distribution of HLA-B alleles in patients with chronic periodontitis.

Distribution of HLA-DRB1 alleles

The distributions of various HLA-DRB[1] alleles among study population were presented in (Table 4). The HLA-DRB[1]14 allele demonstrated a significant higher distribution in control compared with patient (P=0.00) and non-significant distribution of HLA-DRB[1]15 alleles (P=0.1). HLA-DRB[1]13 alleles showed most frequent distribution 46% followed by HLA- DRB[1]3 and DRB[1]11 alleles 41%, whereas, the HLA-DRB[1]12 alleles was recorded the minimum distribution among population study (Table 4).

Distribution of HLA-DRB3, HLA-DRB4 and HLA-DRB5 loci

HLA-DRB[3] and HLA-DRB[4] locus showed non-significant difference between patients and controls. The proportion of HLA-DRB[3] and HLA-DRB[4] loci in chronic periodontitis were 80% and 48.3% compared by 81.5% and 44.4% in controls, respectively. The HLA-DRB[5] loci was significantly higher in control group (18.5%) compared to chronic periodontitis group (3.3%), (P=0.00) (Table 4).

HLA-DRB alleles	Total No. (%)	HLA-B allele patient No. (%)	HLA-B alleles control No. (%)	P-value
DRB[1]13	46 (40.4)	26 (43.3)	20 (37)	0.31
DRB[1]11	41(36)	19 (31.7)	22 (40.7)	0.2
DRB13	41 (36)	23 (38.3)	18 (33.3)	0.36
DRB[1]4	33 (28.9)	16 (26.7)	17 (31.5)	0.53
DRB[1]7	22 (19.3)	14 (23.3)	8 (14.8)	0.18
DRB[1]14	17 (14.9)	4 (6.7)	13 (24)	0
DRB[1]15	16 (14)	5 (8.3)	11 (20.4)	0.09
DRB[1]1	10 (8.8)	5 (8.3)	5 (9.3)	0.41
DRB[1]10	9 (7.9)	6 (10)	3 (5.6)	0.3
DRB[1]8	5 (4.4)	2 (3.3)	3 (5.6)	0.45
DRB[1]12	3 (2.6)	2 (3.3)	1 (1.9)	0.54
DRB[3]	92 (80.7)	48 (80)	44 (81.5)	0.51
DRB[4]	53 (46.5)	29 (48.3)	24 (44.4)	0.41
DRB[5]	12 (10.5)	2 (3.3)	10 (18.5)	0

Table 4: Distribution of HLA-DRB[1] alleles in chronic periodontitis patients.

Discussion

The associations of HLA with chronic periodontitis (CP) have not been previously studied in the Libyan population. In the present study, several variables such as age, blood grouping, gender and race were considered as cofactors in development of CP within population sample. The most of CP cases were ranged between ages 19-62 years and the highest percentage was presented in age group 30-40 years (43.3%). This finding was similar to Newman et al. data, who revealed that 53.7% in age group 30-39 years [11]. Lowest dominance of CP were found in older age groups 41-51years and 52-62 years, 15% and 20%, respectively, this close similar to Grossi et al. surveys in old age patients with periodontal disease at United States, Canada, and Australia, 15%-30% [12].

Chronic periodontitis are prevalent in blood group O+ve (43.3%), while blood group AB and B were not observed. This nearly consistent with Koregol et al. results in Indian patients with periodontitis carried blood group O+ve 32.8% [13] and was not compatible with Sarhan et al. who found blood group B was greater risk for periodontitis [14]. This study revealed that chronic periodontitis common in male gender (63.3%), which consistent with the Albandar et al. findings [15]. Conversely, Reichert et al. noted that gender not vary as a function in HLA and periodontitis studies [16].

The CP was higher in white race 85% nearly compatible to Probst et al. results, who defined that CP is predominantly in white European origin (80.6%), 12.5% in African and 7.0% in Amerindian population [17]. Other study showed that African and Latin American background had a higher risk of developing periodontitis than other groups [18]. Likewise, Albandar et al. study published that African and Mexican American had a greater attachment loss than Caucasians [19]. This can explain that our sample size with black race were limited. Therefore, the increased risk of periodontitis in certain racial/ethnic groups may be partly attributed to socioeconomic and behavioral.

Human leukocyte antigens (HLA) have inconsistent results in aetiopathogenesis of periodontal diseases in several studies [20-23]. Distributions of various HLA-A, B, DRB^1, DRB^3, DRB^4 and DRB^5 genes between patients and controls were variable among this population study. HLA-A30 allele was significantly raised in chronic periodontitis patients with 30% (P<0.04) (Table 2). Therefore, HLA-A30 is an indication of risk marker of Libyan patients with CP. This result was not different with Machulla et al. who light on for high rate of HLA-A30 in patients with periodontitis [22]. This result contrary to Stein et al. who revealed that HLA-A1 and HLA-A3 were trivial in chronic periodontitis in compared with aggressive periodontitis patients [23]. The part of HLA-A34 allele has been found only in CP patients with P<0.1, while the non-significant rates of HLA-A74, 66, 35, 42 and 27 alleles (P<0.2) were presented only in control subjects for the current study. The simultaneous outcome of these markers can be explained that most of HLA-A alleles were not risk factor for chronic periodontitis, with exception, HLA-A30 allele, and may give significant relation when increase population size in further study.

Patients with chronic periodontitis have significantly increased in frequency of HLA-B45 (P<0.03) (Table 3), i.e. probands, who do not carry any of this allele show higher resistance against periodontitis. This may gave rise to hypothesis that HLA-B45 allele was a risk factor for development chronic periodontitis in Libyan population. Furthermore, Stein et al. and Reichert et al. determined that HLA-B5 seems to represent susceptibility factors for aggressive periodontitis [24,25]. Nonetheless, there have been statistical insignificant deviations of HLA-B51, 8, 44, 13, 52, 39, 38, which has been described to be more frequent among controls (P<0.1) and may contribute to higher protection especially towards chronic periodontitis.

Focusing on HLA-DRB^1 target in our study investigation, all alleles that illustrated in Table 4 were closely similar in their distribution between patients and controls subjects, except, HLA-DRB^{1}14 that has significant frequent in control subjects (P<0.02). This result may indicate that HLA-DRB^{1}14 is a protective factor against chronic periodontitis in Libyan population. Bonfil et al. who reported that both HLA-DRB^{1}11 and DRB^{1}14 were lower frequent (3.3%) among patients [26]. Also, other study revealed that the percentage of HLA-DRB^{1}13 and HLA-DRB^{1}3 were 22.9% and 31.2% in control which closely similar to our result, 43.3% and 38.3%, respectively [22,26,27].

Generally, HLA-DRB^{3,4} loci come to pass 80.7% and 46.5% among total population of study, respectively. HLA-DRB^5 locus more frequent in control subjects in compared with patients 18.5% and 3.3%, respectively, (P<0.01). This may contribute protective factor against chronic periodontitis. Contrary to the result, Stein et al. who located HLA-A2 allele was potential protective factor against periodontitis amongst Caucasians individuals [22,28,29].

This study is particular importance as it is a first attempt to study the correlation of HLA alleles with chronic periodontitis in Libya. Further studies have to be carried out in order to investigate the different HLA alleles that present in CP patients [30-32]. This would prove to be an important indication of the risk factors that could be predicted prior to the onset of disease.

Competing interests

The authors state that they have no competing interests.

Authors' contributions

AD designed the study, extracted the data, and drafted and finalised the manuscript. FM & EB analyzed the data and contributed to the drafting of the data. All authors read and approved the final manuscript.

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