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REVIEW ARTICLE

Association between Single Nucleotide Polymorphisms in Interleukin-6 Gene and Periodontal Disease: A Systematic Review and Meta-analysis

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ABSTRACT

Introduction: There has been much discussion recently about the influence of single nucleotide polymorphisms in interleukin-6 (IL-6) gene on periodontal disease in young healthy patients. The aim of the present work is to review the results of each case-control study which fulfills the inclusion criteria, and to perform a meta-analysis to make clear the association between single nucleotide polymorphisms (SNPs) in IL-6 gene and periodontal disease.

Materials and methods: The search process was performed in the main databases in order to find the case-control studies published until August 2014 that matched inclusion criteria. Data were collected and odds ratio (OR) was calculated. Overall statistics was obtained with STATA.

Results: Fifteen studies met the inclusion criteria. There was a lack of data for a proper comprehensive analysis for IL-6 (–373) An/Tm polymorphism and IL-6 (–597) G/A polymorphism. Meta-analysis showed no association between IL-6 (174) GG polymorphism and periodontitis. Similar results were obtained between the IL-6 (–572) SNPs genotype and periodontitis in all patients. A positive association was found when homozygote genotypes were investigated in within studies analysis and in Asian population.

Discussion: Modest evidence of association has been found between interleukin-6 gene polymorphisms and periodontal disease.

Keywords: Cytokine, Genetic, Meta-analysis, Periodontitis.

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INTRODUCTION

Periodontal disease is an inflammatory disorder initiated by the presence of Gram-negative bacteria which results in the destruction of periodontal ligament and alveolar bone.[1,2] This clinical outcome is influenced by several environmental factors[3] but the progression of the disease is different and not predictable in the population.[4] This unpredictability of the progression of the lesion links to genetic factors in host response, i.e. the production of inflammatory markers.[1,5,6] Thus, the production of cytokines by macrophages and neutrophils when a tissue is damaged may be modulated by common nucleotide variations in genes encoding for the molecules.[7-9]

There has been considerable new evidence about the influence of the single nucleotide polymorphisms (SNPs) in gene codifying for cytokine interleukin-6 (IL-6) in host defense.[10,11] Cytokine IL-6 is a pleiotropic molecule involved in the pathogenesis of several inflammatory diseases, such as psoriasis, rheumatoid arthritis and periodontal disease.[12-14] Its major biologic functions when produced by activated macrophages and lymphocytes are to promote terminal differentiation of B cells into plasma cells, stimulate antibody secretion and promote the synthesis of acute-phase proteins in the liver.[15,16] Several case-control studies have been performed in order to clarify the role of the SNPs in the gene encoding for IL-6 located on chromosome 7p21 and contrasting results have been discussed.

The aim of the present work is to review the results of each case-control study which fulfills the inclusion criteria, and to perform a meta-analysis to test the association between SNPs in interleukin-6 gene and periodontal disease.

MATERIALS AND METHODS

Inclusion Criteria and Search Strategy

The inclusion criteria comprised case-control studies conducted in patients with a severe periodontal disease (aggressive, chronic or both) and healthy controls in order to evaluate the association between SNPs in gene encoding for IL-6 and the clinical form of periodontitis. Two independent reviewers (RB and LC) performed the

search under the guide of a librarian in August 2014 reading the title and abstracts of all studies identified. The Cochrane Library, Medline-PubMed, ISI Web of Knowledge, EMBASE, VHL (Virtual Health Library), and gray literature (SIGLE) databases were searched for articles published in English. The main meSH headings and keywords used were: 'periodontitis' or 'periodontal disease' or 'aggressive periodontitis' or 'chronic periodontitis' combined with 'SNP' or 'interleukin-6' or 'genotype' or 'cytokines'. Suitable modifications in the keywords were done to follow the syntax rules of each database. If the abstract contained insufficient information to allow decision making with regard to inclusion or exclusion, the full article was obtained and reviewed before deciding. Any disagreement regarding article selection was solved by discussion. The selected articles were then carefully read for quality assessment and control of bias and for data extraction. In addiction, the reference lists of the included articles, recent reviews and meta-analyses were manually searched.

DATA EXTRACTION

Data on the following issues were extracted from the articles included:

- Author and year of publication
- Form of periodontitis considered
- Ethnicity and health status of the study population
- Gender and smoking habits
- SNPs studied
- Other confounders included in the analyses
- Numbers of cases and controls
- Allele frequencies of IL-6 (–174) G/C polymorphism
- Allele frequencies of IL-6 (–572) G/C polymorphism
- Allele frequencies of IL-6 (–373) An/Tm polymorphism
- Allele frequencies of IL-6 (–597) G/A polymorphism. No missing data were detected.

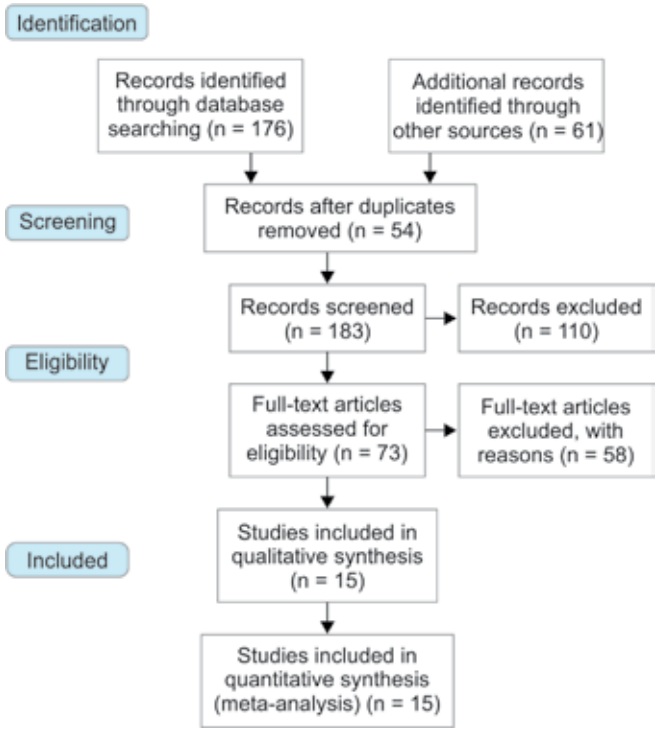
STATISTICAL ANALYSES

We combined comparable data with the meta-analysis. Studies were grouped according to the interleukin gene considered. For each study, the number of cases and controls was tabulated for the different alleles. The results were pooled using the random effects method because the studies compared were not considered to have the same effect size. As Borenstein et al[17] stated the random effects model is generally indicated when studies are gathered from the published literature. The software used in the analyses was STATA 12 (StataCorp 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP). In order to evaluate if observed genotype frequencies conformed to Hardy-Weinberg (H-W) expectations, the Chi-squared p-values were obtained from each study. The strength of association between IL-6 polymorphisms and periodontitis was reported in forest plots and assessed according to odds ratio (OR). Stratification by ethnicity was allowed for all SNPs included. Statistically significant results were declared those with a p-value < 0.05.

RESULTS

The search strategy resulted in 15 studies that met the inclusion criteria as figured in the PRISMA flow diagram (Flow Chart 1).[18-32] However, one of these studies contained data of two different groups, such as aggressive or chronic periodontitis, and they were treated independently.[19] Similarly, Nibali et al[28] divided the analyses and commented the results for each ethnic group included thus preventing us from merging data. Ethnicity of the population were registered and reported in Table 1. The Hardy-Weinberg equilibrium (HWE) was respected for all studies included except five.[19,21,26,31,32] There were three studies that did not show HWE[24,27,29] (Tables 1 and 2). An established risk factor, such as smoking habits, was not recorded and systematically stratified according for genotypes in most of the articles. Thus, there was a lack of data for a proper comprehensive analysis. Only three studies provided data about IL-6 (–373) An/Tm polymorphism and IL-6 (–597) G/A polymorphism. The low number of cases did not allow a reliable meta-analysis about these polymorphisms. Komatsu et al[23] evaluated the association between the IL-6 (–373) An/Tm polymorphism and the susceptibility to chronic periodontitis in Japanese subjects, concluding that the positive relation

Flow Chart 1: Database searching of studies to final inclusion



found should be confirmed by further analyses. Holla et al[21] and Fan et al[30] found not significant association between IL-6 (–597) G/A polymorphism and chronic periodontitis in their case-control study.

Meta-analysis of the Association between IL-6 (174) G/C Polymorphism (RS1800795) and Periodontitis

The meta-analysis comprised 15 studies which included 1695 controls and 1786 patients presenting different single nucleotide polymorphisms in IL-6 (174) G/C (GG/GC/CC). Three comparisons were developed in order to evaluate the influence on the periodontal disease in each ethnic group. Meta-analysis containing all studies showed no association between IL-6 (174) GG polymorphism (RS1800795) and periodontitis (OR = 1.023, 95% CI 0.910–1.149, p = 0.706). Similar results were obtained respectively, with Caucasian and Asian population (Table 3), even if in HWE.

Meta-Analysis of the Association between IL-6 (–572) G/C Polymorphism (1800796) and Periodontitis

The meta-analysis showed no association between the IL-6 (–572) GG genotype and periodontitis in all patients (OR = 1.204, 95% CI 0.930–1.559, p = 0.159). The analysis comprised eight studies (891 controls and 1211 patients). A positive association between IL-6 (–572) polymorphism and periodontitis was found when homozygote genotypes were compared in all studies (OR = 1.660, 95% CI 1.111–2.481, p = 0.013) and in Asian population (OR = 1.570, 95% CI 1.039–2.371, p = 0.032) (Table 4).

DISCUSSION

The present study aimed to collect as many case-control studies as possible and to address the associations between interleukin-6 polymorphisms [(IL-6 (174) G/C, IL-6 (–572) G/C, IL-6 (–373) An/Tm, IL-6 (–597) G/A)] and periodontitis susceptibility. The studies about IL-6 (–597) G/A and IL-6 (–373) An/Tm SNPs which fulfilled the inclusion criteria were not included in the meta-analysis because of the low number of possible comparisons. Fan et al[30] investigated the influence of IL-6 (–597) G/A polymorphisms in Chinese population but the authors did not detect any variant allele A, but only GG homozygotes. Holla et al[21] detected higher frequencies of GA and AA genotypes in Caucasian population but no association with periodontitis susceptibility was revealed. Komatsu et al[23] found a reduced susceptibility to chronic periodontitis and decreased serum IL-6 level when IL-6

Table 1: Characteristics of the studies included in the meta-analysis

Study	*Years*	*Population*	*Form of disease*	*Cases*	*Controls*	*Gene*	*p-value for HWE*
Babel et al	2006	Caucasian	Chronic	122	114	IL-6 (–174) G/C	0.0283
Brett et al	2005	Caucasian	Aggressive	51	100	IL-6 (–174) G/C	0.16
Brett et al	2005	Caucasian	Chronic	57	100	IL-6 (–174) G/C	0.008
Garlet et al	2012	Mixed	Chronic	198	214	IL-6 (–174) G/C	0.2028
Holla et al	2004	Caucasian	Chronic	148	107	IL-6 (–174) G/C	1
Kobayashi et al	2009	Japanese	Not defined	117	108	IL-6 (–174) G/C	0.46
Tervonen et al	2007	Caucasian	Chronic	51	178	IL-6 (–174) G/C	ND
Trevilatto et al	2003	Caucasian	Chronic	48	36	IL-6 (–174) G/C	0.0838
Kalburgi et al	2010	Indian	Chronic	15	15	IL-6 (–174) G/C	<0.01
Nibali et al	2008	Mixed	Aggressive	8	70	IL-6 (–174) G/C	ND
Nibali et al	2009	Caucasian	Not defined	324	144	IL-6 (–174) G/C	0.124
Nibali et al	2009	Blacks	Not defined	93	45	IL-6 (–174) G/C	0.346
Nibali et al	2009	Asian	Not defined	87	29	IL-6 (–174) G/C	0.881
Stefani et al	2013	Mixed	Chronic	21	21	IL-6 (–174) G/C	ND
Fan et al	2011	Chinese	Chronic	178	130	IL-6 (–174) G/C	818
Franch-Chilida et al	2010	Indian	Not defined	152	350	IL-6 (–174) G/C	<0.01
Costa et al	2008	Brazilian	Chronic	38	27	IL-6 (–174) G/C	0.003
Holla et al*	2004	Caucasian	Chronic	148	107	IL-6 (–597) G/A	ND
Fan et al*	2011	Chinese	Chronic	178	130	IL-6 (–597) G/A	ND
Kobayashi et al	2009	Japanese	Not defined	117	108	IL-6 (–572) G/C	ND
Komatsu et al	2005	Japanese	Chronic	112	77	IL-6 (–572) G/C	0.22
Nibali et al	2009	Caucasian	Not defined	324	144	IL-6 (–572) G/C	0.479
Nibali et al	2009	Blacks	Not defined	93	45	IL-6 (–572) G/C	0.236
Nibali et al	2009	Asian	Not defined	87	29	IL-6 (–572) G/C	0.754
Franch-Chilida et al	2010	Indian	Not defined	152	350	IL-6 (–572) G/C	<0.01
Komatsu et al**	2005	Japanese	Chronic	112	77	IL-6 (–373) An/Tm	ND

*IL-6 (–597) G/A not considered; **IL-6 (–373) An/Tm not considered; ND: Not defined

Table 2: Frequencies for each genotype included in the analysis

			Case			Control		
Study	*Years*	*Gene*	*GG*	*GC*	*CC*	*GG*	*GC*	*CC*
Babel et al	2006	IL-6 (–174) G/C	72	0	52	84	0	32
Brett et al	2005	IL-6 (–174) G/C	30	13	6	55	19	25
Brett et al	2005	IL-6 (–174) G/C	22	24	11	55	19	25
Garlet et al	2012	IL-6 (–174) G/C	97	69	32	116	70	28
Holla et al	2004	IL-6 (–174) G/C	43	71	34	37	53	17
Kobayashi et al	2009	IL-6 (–174) G/C	117	0	0	108	0	0
Tervonen et al	2007	IL-6 (–174) G/C	11	0	40	37	0	141
Trevilatto et al	2003	IL-6 (–174) G/C	29	15	4	12	21	3
Kalburgi et al	2010	IL-6 (–174) G/C	10	3	2	2	4	9
Nibali et al	2008	IL-6 (–174) G/C	6	0	2	41	0	29
Nibali et al	2009	IL-6 (–174) G/C	124	142	52	42	74	28
Nibali et al	2009	IL-6 (–174) G/C	81	9	0	38	7	0
Nibali et al	2009	IL-6 (–174) G/C	68	15	2	22	6	1
Stefani et al	2013	IL-6 (–174) G/C	12	8	1	11	8	2
Fan et al	2011	IL-6 (–174) G/C	177	1	0	129	1	0
Franch-Chilida et al	2010	IL-6 (–174) G/C	113	27	10	257	65	16
Costa et al	2008	IL-6 (–174) G/C	31	0	7	12	0	15
Kobayashi et al	2009	IL-6 (–572) G/C	9	50	58	8	40	60
Komatsu et al	2005	IL-6 (–572) G/C	5	36	71	4	32	41
Nibali et al	2009	IL-6 (–572) G/C	2	31	285	0	11	133
Nibali et al	2009	IL-6 (–572) G/C	5	13	68	0	6	39
Nibali et al	2009	IL-6 (–572) G/C	13	38	33	3	13	13
Franch-Chilida et al	2010	IL-6 (–572) G/C	36	69	47	50	143	125

Table 3: Meta-analysis of the association between IL-6 (174) G/C polymorphism and periodontitis

			Test of association			Test of heterogeneity	
Polymorphism	*Population*	*No. of studies*	*OR*	*95% CI*	*p-value*	*Model*	I^2
GG *vs* GC and CC	Overall	17	1.023	0.910–1.149	0.706	R	0
	Overall in HWE	11	1.026	0.891–1.182	0.721	R	0
	Caucasian	7	1.004	0.826–1.221	0.966	R	18.1
	Asian	5	1.033	0.865–1.234	0.718	R	0
GG and GC *vs* CC	Overall	14	0.982	0.807–1.196	0.859	R	22
	Overall in HWE	8	1.075	0.844–1.370	0.557	R	0
	Caucasian	7	1.027	0.814–1.296	0.819	R	13.7
	Asian	3	0.911	0.459–1.809	0.790	R	49.3
GG *vs* CC	Overall	14	1.037	0.830–1.296	0.747	R	61.1
	Overall in HWE	8	0.921	0.694–1.223	0.569	R	33.1
	Caucasian	7	0.940	0.714–1.238	0.661	R	53.7
	Asian	3	1.290	0.645–2.583	0.471	R	77.4

OR: Odds ratio; CI: Confidence interval; R: Random effects model; I^2: Heterogeneity (%)

Table 4: Meta-analysis of the association between IL-6 (–572) G/C polymorphism and periodontitis

			Test of association			Test of heterogeneity	
Polymorphism	*Population*	*No. of studies*	*OR*	*95% CI*	*p-value*	*Model*	I^2
GG *vs* GC and CC	Overall	8	1.204	0.930–1.559	0.159	R	0
	Overall in HWE	6	1.317	0.741–2.340	0.349	R	0
	Caucasian	2	NS	NS	NS	NA	NA
	Asian	5	1.175	0.808–1.707	0.399	R	0
GG and GC *vs* CC	Overall	7	1.132	0.970–1.321	0.115	R	0
	Overall in HWE	6	1.057	0.893–1.252	0.518	R	0
	Caucasian	2	NS	NS	NS	NA	NA
	Asian	5	1.166	0.959–1.419	0.124	R	13
GG *vs* CC	Overall	7	1.660	1.111–2.481	0.013	R	0
	Overall in HWE	6	1.419	0.787–2.558	0.244	R	0
	Caucasian	2	NS	NS	NS	NA	NA
	Asian	5	1.570	1.039–2.371	0.032	R	0

OR: Odds ratio; CI: Confidence interval; R: Random effects model; NS: Not significant; NA: Not available; I2: Heterogeneity (%)

(–373) A9/T11 allele was recorded in Japanese subjects. Regarding IL-6 (174) G/C polymorphism, we did not find an association with periodontitis susceptibility even if stratification for ethnicity was included. We identified similar results for IL-6 (–572) G/C polymorphism both when considering all studies, both when focusing on subjects in HWE. We reported not significant OR, confidence intervals and p-values for Caucasian population because of the low number of studies involved. The analyses with homozygote genotypes IL-6 (–572) GG/CC revealed positive association in all studies subjects (OR = 1.660, 95% CI 1.111–2.481, p = 0.013) and in Asian population (OR = 1.570, 95% CI 1.039-2.371, p = 0.032).

Meta-analysis cannot correct all the biases of individual studies but it generates a statistical conclusion with larger power and precision.[33] The local literature bias is a limitation for this meta-analyses. Asian authors published interesting studies developed in different ethnic groups but their results remain not accessible to researchers and clinicians.[34-37] Moreover, case-control studies are subject to limitations, such as the limited size of subjects sample, the existence of heterogeneity in periodontitis definition, the inclusion of potential confounders.[38]

On the contrary, our meta-analysis confirmed a low heterogeneity (I^2) among the studies, mainly when IL-6 (–572) G/C polymorphism was investigated. I^2 reflects the extent of overlap of confidence intervals, thus, being a measure of consistency across findings of the studies.[17] In addiction, we assessed the impact of deviations from HWE[39] and we compared the results with the overall, even if they did not reveal significant findings.

As interleukin-6 gene polymorphisms increase IL-6 expression in endothelial cells, fibroblasts, and macrophages, IL-6 (–572) G/C may be related with the pathogenesis of periodontitis, mainly when homozygosity occurs. Several studies described the crucial role of IL-6 in the inflammatory response to Gram-negative bacteria[40] by affecting the composition of the subgingival microbiota thus increasing the susceptibility to colonization with periodontopathogenic bacteria and by stimulating osteoclast differentiation and bone resorption.[41,42]

CONCLUSION

We found that IL-6 (–572) G/C polymorphism is associated with a modest increase in the probability of developing periodontal disease. However, periodontal disease has a multifactorial etiology which combines genetic and environmental causes. Thus, future case-control studies should take into account the environmental factors (such as infection by specific bacteria at high levels, smoking and poorly controlled diabetes mellitus), focus on single gene polymorphisms and replicate the methods on different ethnic groups in subsequent studies. Consistent meta-analysis results on other single nucleotide polymorphisms on a specific gene should foresee further analyses that address simultaneously the combined effect of two or more SNPs.

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