THE ASSOCIATION BETWEEN TUMOR NECROSIS FACTOR-ALPHA (TNF-α) GENE POLYMORPHISM AND SUSCEPTIBILITY TO DIFFERENT FORMS OF PERIODONTAL DISEASE

Thesis

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A :	**Adenosine**
A. a. :	**Aggregatebacter actinomycetem comitans**
ACE :	**Angiotensin converting enzyme**
AF :	**Amniotic fluid**
AIDS :	**Acquired Immunodeficiency Syndrome**
B-cells :	**B-lymphocytes**
BD :	**Behcet's disease**
C :	**Cytosine**
C2 :	**Complement component 2 gene**
C4 :	**Complement component 4 gene**
CAL :	**Clinical attachment loss**
CCL :	**C-C Chemokine Ligand**
CCR :	**C-C Chemokine Receptor**
CD14 :	**Cluster of differentiation 14**
CEJ :	**Cemento-enamel junction**
Ch6 :	**Chromosome 6**
CIs :	**Confidence intervals**
CTLA4 :	**Cytotoxic T-lymphocyte antigen 4**
DNA :	**Deoxyribonucleic acid**
EOP :	**Early-onset periodontitis**
FcγRIIB1 :	**Fc-gamma receptor type II B1**
G :	**Guanine**
G-EOP :	**Generalized early-onset periodontitis**
GCF :	**Gingival crevicular fluid**
GI :	**Gingival index**
GM-CSF :	**Granulocyte monocyte -colony stimulating factor**
HIV :	**Human Immunodeficiency Virus**
HLA :	**Human Leukocyte Antigen**
HSP :	**Heat Shock Proteins gene**

IBDs :	**Inflammatory bowel diseases**
IL:	**Interleukin**
IL-1RA :	**IL-1 receptor antagonist**
IL-5Rα :	**IL-5 receptor alpha**
IL-6R :	**IL-6 receptor**
IL-12 R :	**IL-12 receptor**
IDDM :	**Insulin-dependent diabetes mellitus**
IFNγ :	**Interferon gamma**
JRA :	**Juvenile Rheumatoid Arthritis**
LPS :	**Lipopolysaccharides**
LST.1 :	**Leukocyte-specific transcript 1 protein**
LT :	**Lymphotoxin**
MHC :	**Major histocompatibility complex**
MHC-I A :	**MHC class I A antigen locus**
MHC-I B :	**MHC class I B antigen locus**
MHC-I C :	**MHC class I C locus**
MHC-I G :	**MHC class I G locus**
MHC-II DP :	**MHC class II DP locus**
MHC-II DQ :	**MHC class II DQ locus**
MHC-II DR :	**MHC class II DR locus**
MMPs :	**Matrix metalloproteinases**
NIH GAD :	**NIH Genetic Association Database**
NK cells :	**Natural killer cells**
NOS 3 :	**Nitric oxide synthase 3**
Nramp :	**Natural resistance-associated macrophage protein**
OMIM :	**Online Mendelian Inheritance of Men**
OPG :	**Osteoprotegrin**
ORs :	**Odds Ratios**
P. gingivalis :	**Porphyromonas gingivalis**
PCR-RFLP :	**Polymerase Chain Reaction-Restriction Fragment Length Polymorphism**

PGE2 :	**Prostaglandin E2**
PI :	**Plaque index**
PTB :	**Preterm birth**
R-allele :	**Rare allele**
RA :	**Rheumatoid arthritis**
RAS :	**Recurrent Aphthus Stomatitis**
RFLP :	**Restriction Fragment Length Polymorphism**
SD :	**Standard deviation**
SLE :	**Systemic Lupus Erythematosis**
SNP :	**Single nucleotide polymorphism**
sPTB :	**Spontaneous preterm birth**
SS :	**Sjogren's syndrome**
STRs :	**Simple tandem repeats**
T :	**Thymine**
Taq :	**Thermus aquaticus**
T-cells :	**T-lymphocytes**
TB :	**Tuberculosis**
TBE :	**Tris-borate EDETA**
TGF β :	**Transforming growth factor beta**
TNF :	**Tumor necrosis factor**
TNFRs :	**TNF receptors**
TP 53 :	**Tumor protein 53**
Tpm1 :	**T-cell phenotype modifier-1**
VNTRs :	**Variable number of tandem repeats**

Abstract

This study was performed on 160 patients, divided into four groups, 40 normal healthy controls, 40 suffering from gingivitis, 40 suffering from chronic periodontitis and 40 suffering from aggressive periodontitis.

The results suggested that GG genotype is associated with chronic periodontitis in Egyptian patients and that harboring the G allele is associated with the development of aggressive periodontitis and chronic periodontitis.

Key words: TNF-α, Cytokines, Gene Polymorphism, Periodontitis

المستخلص

أجريت هذه الدراسة على ١٦٠ مريضا ، وتنقسم الى أربع مجموعات ، و ٤٠ من الاصحاء ، و ٤٠ يعانون من التهاب اللثة ، و ٤٠ يعانون من التهاب الأنسجة الداعمة للأسنان المزمن و ٤٠ يعانون من التهاب الأنسجة الداعمة للأسنان العدواني .

النتائج رجحت أن النمط الجينى GG مرتبط بحدوث التهاب النسيج الداعم للاسنان المزمن لدى المرضى المصريين وان مرور اليل G يرتبط بظهور التهاب النسيج الداعم للاسنان المزمن والعدوانى فى المصريين.

الكلمات الدالة: عامل التنكرز-ألفا ، السيتوكينات ، تعدد موروثة الجين، التهاب اللثة

INTRODUCTION AND REVIEW OF LITERATURE

Periodontal diseases are chronic inflammatory conditions which result in loss of the tooth-supporting structures including osteoclastic resorption of alveolar bone in the jaw ***(Page and Schroeder, 1982).***

Periodontal diseases comprise a variety of conditions affecting the health of the periodontium. Although the classification scheme defined at the 1989 World Workshop in Clinical Periodontics subdivided these diseases into a number of clinically defined subforms, subsequent attempts to categorize patients according to the defined criteria have demonstrated the considerable problem of overlap in the disease definitions ***(Armitage, 1996).***

Later on, periodontal diseases were classified into gingivitis, chronic periodontitis, aggressive periodontitis, periodontitis as a manifestation of systemic disease, necrotizing periodontal diseases, periodontal abscess, periodontitis with endodontic lesions and finally, developed and acquired deformations and conditions ***(ADA classification, 1999).***

Research dating back to the 1980s has shown that relatively few sites with gingivitis go on to develop periodontitis ***(Listgarten et al.,1985; Haffajee et al., 1988; Okamoto et al.,1988; Lindhe et al., 1989; Machtei et al., 1999; Kornman, 2001).***

Clinical models of disease activity in periodontitis range from a continuous progression of disease during which loss of attachment

occurs at a slow rate over long periods of time to an episodic burst model in which loss of attachment occurs relatively rapidly during short periods of disease activity ***(Socransky et al., 1984; Jeffcoat and Reddy, 1991; Reddy and Jeffcoat, 1993).***

Development of gingivitis requires the presence of plaque bacteria ***(Löe et al., 1965; Theilade et al., 1966),*** which are thought to induce pathological changes in the tissues by both direct and indirect means ***(Page, 1986).***

The early vascular changes occur in the periodontium, with exudation and migration of phagocytic cells, including neutrophils and monocytes/macrophages, into the junctional epithelium and gingival sulcus, resulting in initial gingival inflammation. These changes are accompanied by increases in the size of the connective tissue infiltrated by leukocytes, loss of perivascular collagen fibres, and proliferation of junctional epithelium. During the early stage, the inflammatory infiltrate is mostly T-cells, whereas in the established lesions, B-cells become the most common inflammatory cells ***(Page and Schroeder, 1976).***

The contribution of the acquired immune cells in the progression of periodontal disease has long been controversial, with its exact role in the protection versus destruction of the host's periodontium being unclear ***(Klausen, 1991; Ebersole and Taubman, 1994; Zambon, 1996).***

Although direct evidence for specific mechanisms explaining the appearance and progression of gingivitis lesions is not available, the chronic inflammatory infiltrate characteristic of the early and