GENETIC POLYMORPHISM TNF- α GENE OF GUM DISEASE IN PATIENTS WITH DIABETS MELLITUS (TYPE2)

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Abstract: Approximately 400 million people worldwide suffer from diabetes, and this number will increase by about 50% by the year 2030. Gingivitis, is a gum disease of the teeth, which is part of the periodontium, supports the teeth. It is estimated that severe periodontal disease affects about 19% of the world's adult population and represents more than 1 billion cases worldwide. In the description WHO Oral Health Status Report (2022) poor oral hygiene and tobacco use are the most common factors for periodontal disease. There is evidence that there is an association between these two chronic conditions. Although studies have been conducted on the immune system and its components, mechanisms have not been fully understood. This article will discuss associations between diabetes and oral health, focusing on periodontal diseases, find relation genetic polymorphism in TNF-alpha gene.
Keywords*:* diabetes, gum disease, diabetus mellitus type 2, TNF-α gene, genetics of diabetes

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I. Introduction

Gingivitis is an inflammatory disease of the gum tissue, which is a component of the periodont that surrounds the tooth. Although the etiology includes the microflora of the oral cavity, changes in the body's metabolism and external environmental factors increase the risk of disease. We can see the most prominent effect of metabolic dysfunctions in the case of diabetes. Diabetes is a disease that is common against the background of hyperglycemia due to lack or lack of insulin hormone or inability to use it. In 1998, 4 types of forms were approved by the American Diabetes Asossation. Of these, although idiopathic and gestational diabetes are less common, type 1 and Type 2 have become a kind of epidemic [1]. It should also be noted that, in 1935 Hinsworth identified 2 types of diabetes, for almost 2000 years it has been identified as just 1 disease. Both common types of diabetes are characterized by a persistent increase in its glucose in the blood plasma, but type 1 diabetes (T1D) is an autoimmune disease that causes the complete loss of insulin-producing cells in the pancreatic islets, type 2 diabetes (T2D) occurs due to increased resistance to insulin circulating in target tissues (especially muscle, liver and fat) despite insulin secretion from the islets [2].

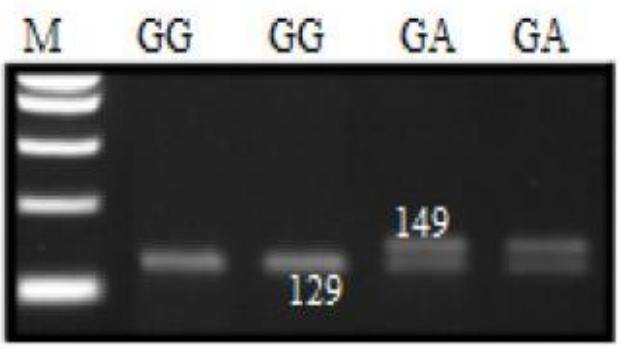
Etiopathogenesis of gingivitis

Quantitatively hundreds of thousands of bacteria colonize the oral cavity in lifetime [3]. The quantitative balance, which changes due to the existing status of the organism, does affect the soft tissues of the oral cavity including the gingiva. Mainly gram negative and gram positive bacteria are responsible for inflammation of the gum tissue. These bacteria secrete lipopolysaccharide endodoxins, stimulating

magrophages that cause gingival destruction, synthesizing interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α), prostaglandin E2 (PGE2) [4]. Hyperglycemia in diabetes has been shown as an important risk factor for the manifestation of vascular complications. The five classic complications associated with T2D include retinopathy, neuropathy, nephropathy, cardiovascular complications (coronary arterial disease, stroke, and peripheral vascular disease), and chronic wound healing. Periodontal disease has recently been recognized as the *"sixth complication"* of type 2 diabetes [5] . As a manifestation of this complication, we can see accumulation non-enzymatic glycolysis products (AGE-advanced glycation end-products) and activation of sensitive receptors (RAGE – receptor advanced glycation end-products). These receptors are located on neutrophils and macrophages, which provide stimulation of phagocytic activity during inflammation. Under the influence of diabetes, proteins such as collagen, lipids, nucleic acids ,entering into non-enzymatic glycolysis and oxidation with aldose sugars, configuring irreversible molecular structure, which accelerates vascular wall permeability, immune response IL-1 and TNF-α hyperactivity, synthesis of IgA and IgG, leading to intensive disintegration of gums and surrounding tissues [6].

II. The role of TNF-α

TNF-α is mainly produced by macrophages. It is an effective immuno-inflammatory mediator and can promote bone resorption by activating the maturation of osteoclasts (bone-destroying cells). Stimulates the production of related cytokines, increases the adhesion expression of molecules, promotes the activation of neutrophils and T cells. It plays a key role in the pathogenesis of some serious chronic inflammatory and autoimmune diseases [7]. A Meta-analysis showed that TNF-alpha can be used as an additional criterion for a more accurate diagnosis of periodontal inflammation. Single nucleotide polymorphisms SNPs are the most common type of genetic variation in humans.. Studies have shown that single nucleotide polymorphisms, specifically the transition from G to A at position 308, increase TNF-a production fivefold in vitro [8]. Tumor necrosis factor alpha (TNF-α) is a proinflammatory cytokine that has an important role in the pathogenesis of a several diseases. The gene encoded by is located on the short arm of chromosome 6p21.3 (Figure 1), in the region of the main histocompatibility complex (MHC)Class III. Most TNF-α gene polymorphisms are located in its promoter region and are believed to affect the susceptibility or severity of various human diseases. This review summarizes data on the relationship between the TNF-α gene and its receptor polymorphisms and the development of autoimmune diseases. Genetic changes in the promoter region can regulate TNF-α production, transcription, and affect susceptibility to inflammation-related diseases.



Some studies have investigated single nucleotide polymorphisms in the promoter region of the TNF gene, such as 238G/A, 308G/A, 857C/T, and 1031T/C in humans. *Although several studies have focused on the relationship between the TNF-α-308g/a polymorphism and T2DM, their results remain uncertain, leading to the need for further research.* It plays a central role in the development of T2DM, according to research by Feng, Y.Li, and others [9]. Swetha Chikoti, Umme Najiya and others was determined polymorphism of the TNF-alpha gene -308 G/A according to a study of 400 patients in the southern Indian population. As a result among 200 T2DM and 200 control patients, gender, age, sugar, cholestorol values were studied and statistical analysis was carried out. Genotyping was studied at these loci −238G/A; rs361525 and −308G/A; rs1800629. gel-agarose results of the rs1800629 locus GG / 129 n.c. GA / 149 n.c. (Figure 1) are monitored. Allele and genotype frequencies for all SNPs were calculated using the Chi-square criterion [χ2] to estimate intergroup significance. The risk of disease by genotype was determined by determining the odds ratio (OR) with a confidence interval (CI) of 95%, respectively (Figure 2). The G / A genotype increased more than 2 times (1.70-3.85) in relation to others [10].

SNP	Genotypes				HWE	Alleles				Odds ratio	
rs1800629 (−308G/A)	AA (%)	GA (%)	GG (%)	χ^2 (p-value)	χ^2 (p-value)	G	A	χ^2 (p-value)	Group comparison	OR 95 % CI	p value
HC (200)	84 (42)	93 (47)	23 (11)	18.21 (0.0001)	0.13 (0.71)	0.35	0.65	0.005 (0.94)	AA vs. others	0.50 (0.33–0.76)	0.001
T2DM (200)	53 (26)	135 (68)	12 (6)		33.5 (0.000)	0.40	0.60		GA vs. others	2.56 (1.70–3.85)	0.00001
									GG vs. others	0.49 (0.23–1.02)	0.09

It has been widely researched that Periodontal disease is one of the main causes of tooth loss in people with diabetes. Individually, many mechanisms have been proposed that explain the increased susceptibility to periodontal disease in patients with unchecked T2D, including changes in collagen metabolism and vascular wall. In addition, poorly controlled T2D patients show an excessive inflammatory reaction to the bacterial hazard of periodontitis. Such hypersensitive reactions lead to a delay in the regeneration of intra-oral tissues, the completeness of which is impaired against the background of increased inflammation, as well as to the degeneration of periodontal tissues [11]. A small percentage of non-autoimmune diabetes (5% or less) is caused by monogenic causes and is classified as juvenile or MODY(monogenic diabetes of the young) monogenic diabetes. These changes are caused by individual high penetrance genes, in which mutations in the nuclear factor-1a (HNF-1a) and Glucokinase (GCK) gene of hepatocytes are most common. These forms of diabetes are sometimes mistaken for T2D, but they are different diseases in terms of their clinical course. Decommunization is important, considering that the boundaries between polygenic and monogenic forms are not always clearly defined at the genetic level [12]. Poulami, Keheibamding and their colleagues found that single nucleotide polymorphism of this gene (TNF-afla) is found in the aggressive course of gum disease. So, as a result of research on 397 people, SNPs were detected. In this study, 40 people were identified as patients with

aggressive periodontitis, 157 as patients with chronic periodontitis, and 200 as healthy controls. The study, conducted among both women and men of different age groups (Table 1), characterizes the population of the East-India region. Five SNPs of the promoter site of the TNF-alpha gene, (rs361525, rs1800629, rs1799724, rs1800630 and rs1799964) were genotyped by PCR sequences in patients with periodontitis and control group. The aim is to find out the relationship of polymorphisms of the TNF-alpha gene with both chronic and aggressive periodontal diseases in the Indian population and to analyze the combination and distribution of haplotypes in acute and chronic periodontitis in both populations of patients.

As a method, the current state of the oral cavity of individuals in this population including gingiva and bone melting was evaluated and indexed by evaluating gingival pockets on all teeth, (Table 2) and on the gene-238G/A (rs361525) polymorphism F-5` CAGTGGGGTCTGTGAATTCC3` R-5`TCCCTCTTAGCTGGTCCTCT3`,-308G/A(rs1800629) F-5` CAGTGGGGTCTGTGAATTCC3` ; R-5`GGGCGGGGAAAGAATCATTC3`, -857C/T (rs1799724) F-5` CTGCTTGTGTGTGTGTCT 3` R-5` CCGGAGACTCATAATGCTGGT3` -863C/a (rs1800630) and - 1031T/C (rs1799964) respectively F-5` GTGTGTGTCTGGGAGTGAGA3`; R-5` GCAGGCCTTCTTCTTCATTCT3`, F-5` GAGAGAAAGAAGTAGGCATGAGG3` R-5` TCTTAAACGTCCCCTGTATTCCA3` amplified by PCR method using primer sets.

Parameters	*AP*	*CP*	*Kontrol*	*AP vs Control (Pvalue)*	*CPvsControl (Pvalue)*
Age (year)	17-44	22-69	24-65		
Average	30,23± 6,81	41,59± 11,12	38,41± 9,48	0.0001	0.0038
Man(%)	60	65,33	47,5	0,1515	0,0016
Woman(%)	40	34,67	52,5	ref.	ref.

Table 1. Age, gender parameters of patients in the study (AP-agressive periodontitis, CP-chronic periodontitis, P<0,05)

Parameters	Aggressive periodontitis	Chronic periodontitis	Control
GP *(all teeth,ave. ±mm)*	6.01± 1.94	6.36 ±1.62	0.34 ±0.66
BR *(ave. ±mm)*	8.3±2.21	8.79±1.94	0.03±0.21
DI	2.83±1.08	2.95±0.81	0.05 ±0.2
GI	3.05 ±0.85	2.61±1.01	0.01±0.08
P value <0,05			

Table 2. Gingiva rates in patients (GP-gingival pocket, BR-bone resorbtion, TP-tooth plaque index, Gİ-gingival index)

Amplified solutions were electrophoresized in 2-3% agarose gel. The PCR products were sequenced (by the Sanger method) by the Prism 3100 DNA Genetic Analyzer (biosystem, Carlsbad, CA, USA).

The difference between clinical parameters was assessed using a single - factor analysis-ANOVA. Age, gender, ethnicity, smoking, chewing tobacco, and the habit of drinking tea have been used as independent variables for their multiple analysis. All statistical analyses were performed with commercially available SPSS software (version 16.0, SPSS Inc., Chicago, Illinois, USA).

Genotypes – 238 G/A (rs361252) and – 308G/A in the AP population as well as polymorphisms-308G/A and-1031T/C (rs1799964) in the CP community are interrelated and are likely to be passed down from generation to generation. The genotype level of TNF-alpha-308 G/A (rs1800629) was significantly higher in patients with both AP and CP compared to healthy control groups [13]. Several studies have been conducted to assess the relationship between TNF-a promoter polymorphisms and periodontitis in different populations, but this is still a matter of controversial discussion [14,15]. There are several contradictions regarding the TNF-a gene as a candidate for genetic studies related to gingivitis and complications. There is reason to believe that the TNF-a gene plays an important role in the pathogenesis of periodontitis, since it is a powerful immunological mediator with anti-inflammatory properties [16].

III. Conclusion

Consequently, the TNF-alpha gene, which controls inflammatory processes and plays a leading role in the formation of immune response reactions, manifests itself with complications when exposed to polymorphism of the promoter region -308 G/A in both patients with gingivitis and patients diabetes mellitus with poor sugar control.

Abbreviation: T2DM - type2 diabetus mellitus, TNF -tumor necrosis factor, HWE - Hardy-Weinberg Equilibrium

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