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Influence of gene polymorphism of IL-13 and smoking on periodontitis

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Abstract

Periodontitis is a multifactorial disease with episodes of exacerbation and remission, mediated by the immune response of the host. The pathogenesis of the periodontal disease is disturbing the interest of many investigators in order to find the mechanisms accelerating the destructive process. The cytokines are found to be involved in the host response. Recently the single nucleotide polymorphisms are introduced as a marker for different inflammatory, autoimmune and malignant diseases. According to some researches Interleukin-13 single nucleotide polymorphism is considered a risk factor for developing severe periodontitis. Since the genetic predisposition differ between individuals and among different populations studies are aimed at finding a connection relating this cytokine and its genetic polymorphism with the periodontal disease.

Keywords: periodontitis; pathogenesis; Interlekin-13; single nucleotide polymorphism

Introduction

Periodontitis is a complex disease that is considered to be the leading cause of tooth loss in elderly individuals. Initiation of periodontitis is mediated by pathogenic bacteria in subgingival bacterial plaque, but is modulated by the host's response in susceptible patients. The periodontal pathogens persist and periodically attack the body, stimulating the immune response and in some individuals this interaction between microorganisms and host progresses to clinical attachment loss and alveolar bone loss, which are definitive signs of periodontitis. The risk of disease does not depend on the amount of plaque itself, although it is a key factor in the initiation of the disease itself, but on various factors, including environmental factors and genetic predisposition. The gene polymorphisms are thought to have a predisposing role in the progression of periodontitis. Scientific research in recent decades has made it possible to identify suspect genes that are considered to be risky or protective in relation to the disease [1].

Interleukin-13 (IL-13) is a proinflammatory cytokine which is upregulated in the periodontal disease and has the ability to supress the inflammatory processes. It is a Th2 cytokine with pleiotropic action produced by many cell types and has a wide range of functions [3]. Interleukin-13 has proven and numerous effects on fibroblasts, including the expression of periostin, integrins and proliferative factors, as well as on cells of a non-immune nature, by initiating eotaxin production and increasing the contractility of bronchial smooth muscle cells. It has a major role in the development of systemic sclerosis, asthma and gastrointestinal inflammatory diseases. The scientific knowledge is now aware that IL-13 is a potent mediator of Th2 inflammation [4].

The gene of the human IL-13 is located on chromosome 5q31-33 [5]. IL-13 is produced by the Th2 lymphocytes. It has the ability to supress the proinflammatory mediators, regulates the collagenogenesis and in general is consideres as a pluripotential cytokine [6]. It was established that its expression was found in periodontal lesions, but not in a healthy tissues [7]. There are a conflicting data showing that expression of IL-13 is found in healthy periodontal tissues [8].

IL-13 plays a critical role in the pathogenesis of asthma, rhinosinuitis, colitis, inflammatory bowel disease etc. [9-11]. The scientific interest is directed to the new possibilities to utilise the cytokines as a marker for periodontitis [12].

A significant modifying factor of periodontitis is the tobacco smoking. There are solid data proving the harmful role of nicotine in the occurrence of various diseases in the oral cavity, including periodontitis [13]. The smokers have more severe periodontal destruction compared to non-smokers. The smoking has negative impact on the wound healing after surgical periodontal treatment, but also after non-surgical therapy [14].

Both genetic and environmental factors play a role in the development of the clinical expression of the disease. Regarding the key importance of the microbial factor, there are sufficiently convincing scientific studies proving the importance of pathogenic microorganisms in the initiation of the inflammatory process. Gene variations are specific to each individual, but share commonalities at the population level [1]. That particular argument is driving the interest of our team toward IL-13 presence in a Bulgarian population and its significance regarding the severity of periodontitis.

Aim

To investigate the presence of gene polymorphism for interleukin-13 at position (-1112) in patients with periodontitis and healthy probands in a Bulgarian population. In accordance with the aim we are trying to relate the presence of the polymorphism to the severity of periodontitis.

Materials and Methods

101 individuals were included in the study after signing an informed consent. The study is approved by KENIMUS.

Inclusion criteria:

- For healthy volunteers - adults, unrelated; systemically healthy; without signs of periodontitis; PD ≤ 3mm
- For patients with periodontitis – systemically healthy, unrelated, no periodontal treatment in the last one year, no antibiotics and anti-inflammatory drug intake, presence of PD ≥ 7 in at least 4 teeth, presence of CAL ≥ 5mm in more than 30% of the investigated sites (generalised periodontitis), presence of severe periodontitis with rapid rate of progression according to the Classification of periodontal and peri-implant disease and conditions 2017 Stage III Grade B), presence of bone loss.

For all included individuals - lack of orthodontic treatment, lack of taking antibiotics or non-steroidal anti-inflammatory drugs at least one year before participating in the project.

Exclusion criteria: close related individuals, pregnant and lactating women, individuals with orthodontic appliances, patients on systemic medication, patients with malignancies or systemic diseases.

To all of the participants periodontal diagnosis was performed including hygiene status and gingival status, registered by Full Mouth Plaque Score (FMPS) and Full Mouth Bleeding Score (FMBS), Probing Pocket Depth (PPD), Clinical Attachment Loss (CAL), Bleeding on Probing (BoP), Furcational involvement (F), Mobility (M) and Recessions (R). The diagnosis periodontitits was confirmed radiographically. PPD and CAL were measured circimferential around all teeth and the deepest values were recorder in six sites in a periodontal chart. BoP was recorded in six sites. All measurement were performed by UNC 15 Hu Friedy periodononta probe.

The DNA from all of the participants was collected with the ‘buccal mucosa sample’. The RFLP PRC analysis was performed in National Genetic Laboratory by utilisation of a Nucleo Spin MACHEREY-NAGEL kit with columns. Protocol for isolation of genomic DNA from buccal mucosa:

- Remove the brush and spin the sample at 12,000 rpm for 10 min. Remove the supernatant and resuspend the cells with part of the water;
- Pre-lysis - add 180 µl T1 buffer and 25 µl proteinase K;
- Vortex and incubate at 56°C for 1-3 hours;
- Lysis - Add 200 µl B3 buffer and incubate at 70°C for 10 min;
- Add 210 µl 96-100% ethanol and vortex;
- The sample is transferred to the column and spun at 11,000 g for 1 min;
- Add 500 µl BW wash buffer and spin at 11,000 g for 1 min;

- Add 600 µl W5 wash buffer and spin at 11,000 g for 1 min;
- Dry spin at 11,000 g for 1 min;
- Elution of the sample - The column is placed in the pre-labeled 1.5 mL ependorf tube. Add 80 µl of BE buffer. Incubate at room temperature for 1 min and spin at 11,000 g for 1 min;
- Pre-analytical processing – PCR (polymerase chain reaction) and sample evaluation on 2% agarose gel;
- Analysis - RFLP (Restriction fragment length polymorphism) - a method for detecting variants (polymorphisms/genetic markers) in the DNA molecule by restriction of the DNA fragment using restriction enzymes that recognize the specified region. This results in different length fragments of the PCR product and can thus be analysed. Analysis is done after running the samples on a 3% agarose gel.

PCR Amplification

The upstream primer sequence was 50-ACTGGGGCTTGGGGTGATC-30, and the downstream primer sequence was 50-ATGCCTCTGAGCGGGAATC-30. PCR was performed in a 25-ll reaction mixture containing 1.5 µl of upstream and downstream primers, 2.0 µl of template DNA, 2.5 µl of MgCl2, 0.5 µl of dNTPs, 2.5 µl of 109 PCR buffer, and 0.2 µl of Taq DNA polymerase. The PCR condition included pre-denaturation for 4 min at 94° C, denaturation for 30 s at 94 C, annealing for 30 s at 66° C, and extension for 30 s at 72° C. The last three steps were repeated for 35 cycles, followed by final extension for 5 min at 72 °C. PCR yielded an amplicon of 393 bp.

Restriction Fragment Length Polymorphism (RFLP)

Ten microliter of the PCR product was digested in a reaction mixture that contained 2 µl of restriction enzyme Ncol, 2 µl of 109 digestion buffer, and water for the final volume of 30 µl. The reaction was carried out in a water bath for 16 h at 37° C.

DNA Electrophoresis and Genotype Determination

Ten microliter of the digested product were mixed with 1 µl of bromophenol blue and xylene cyanide, and electrophoretically separated on 2 % agarose gel containing ethidium bromide (65 min at 95 V). Gels were observed under UV illumination. The presence of the CC genotype yielded a band of 393 bp, the TT genotype produced a band of 198, and the heterozygous CT genotype resulted in the appearance of two bands of 198 and 393 bp [15].

The statistical data were implemented by the statistical package PCA – IBM SPSS Statistics Version 22. The level of significance at which the zero hypothesis is rejected will be $p < 0.05$.

1. Descriptive analysis – the frequency distribution of the studied parameters is presented in tables divided into subgroups.
2. Student T-test – for testing hypotheses of two independent parameters. The significance level is 0.05.
3. Correlation coefficients – to measure the strength/tightness of the relationship between different parameters.
4. $\chi 2$– a method of testing hypotheses for the presence of a statistically significant relationship between two variables located on weak scales

Results

Among the tested individuals 30 of them have diagnosis periodontal health and 71 have severe periodontitis.

Table 1. Basic characteristics in all participants.

Characteristic	Meaning	Relative share
Base (number of participants)	*N=101*	
Gender	Male	47,2%
	Female	52,8%
Tobacco smoking	No	57,5%
	Yes	42,5%
SNP of IL13 -1112 (rs1800925) C>T	TT	1,0%
	CC	82,2%
	CT	16,8%
Periodontal health status	Periodontitis	70,7%
	Periodontal health	28,3%

We have tested 101 individuals with a mild prevalence of female participants compared to male (52,8% vs 47,2%). According to the smoking habit 42,5% are smokers and 57,5% are non-smokers. Among the selected sample we have included 70,7% patients with severe periodontitis and 28,3% healthy volunteers. The genotyping revealed a presence of three different genotypes: CC genotype (83%), CT genotype (16%) and only 1% TT genotype.

The TT genotype individual is female, 60 years old, patient with periodontitis, non-smoker. Since no statistical analysis could be performed in one individual with TT genotype all of the statistical data includes 100 individuals – with CC and CT genotype.

The following parameters related to hygiene status, gingival status and periodontal status will be presented with statistics in the manuscript: FMPS, FMBS, PD 1-3mm, PD 3-5mm, PD 5-7mm, PD > 7mm, CAL 1-2 mm, CAL 3-4mm, CAL ≥ 5mm, BoP, BI/Age.

The descriptive statistics shows in the table the mean age of the periodontitis patients is 48.4 years with the lowest detected age of 29.0 years and the highest of 86.0 years. The average value of dental plaque prevalence registered by FMBS is relatively high – 85.57% covered with dental plaque surfaces. The inflammation caused by the presence of the plaque at the gingival margin is established by FMBS and represents b66.24% average value. The shallow periodontal sites (PD 1-3mm) have an average prevalence of 46.02% of all sites measured. Periodontal sites with a PD 3-5 mm have a mean value of 32.76%. The periodontal pockets with a probing depth of 5 to 7 mm represent an average value of 14.63% of all sites examined, and the deepest periodontal pockets showing values of more than 7 mm probing depth (PD ≥ 7 mm) have an average value of distribution of 6.58% of all measured periodontal sites. The sites with mild clinical attachment loss - CAL 1-2 mm, has average value 23.77% from all of the measured periodontal sites.

Table 2. Periodontal parameters for the patients.

Tested parameter	*N*	Average	Median	Standart deviation	Range	Minimal value	Maximal value
Age	70	48,4	47,0	11,8	57,0	29,0	86,0
FMPS (%)	70	85,57	89,50	16,95	72,10	27,90	100,00
FMBS (%)	70	66,24	64,25	26,77	81,20	18,80	100,00
PD 1-3 (%)	70	46,02	43,00	19,11	79,70	9,00	88,70
PD 3-5 (%)	70	32,76	34,25	15,04	67,00	7,00	74,00
PD 5-7 (%)	70	14,63	12,35	9,47	40,40	0,60	41,00
PD ≥7 (%)	70	6,58	5,00	7,79	51,90	0,00	51,90
CAL 1-2 (%)	70	23,77	23,00	18,42	69,10	0,00	69,10
CAL-3-4 (%)	70	33,48	32,65	17,26	86,00	0,00	86,00
CAL ≥ 5 (%)	70	34,96	33,80	20,52	98,20	1,80	100,00
BOP (%)	70	82,35	84,00	17,56	70,60	29,40	100,00
BL/AGE	70	1,04	1,09	0,35	1,80	0,34	2,14

Periodontal sites characterized by moderate clinical attachment loss represent 33.48%, and sites with severe clinical attachment loss are found to be 34.96% of all examined sites. High values were registered for the parameter indicating periodontal pocket activity/inflammation (BoP) – 82.35% average value, which means that inflamed periodontal pockets represented 82.35% of the examined sites in the patients with periodontitis. Values above 1 are found in relation to the bone loss index in relation to the patient's age - Bl/Age - the average value is 1.04, with the highest recorded value being 2.14.

Table 3. Genotype and allele distribution.

	Health Status								
	Periodontitis		Periodontal health		p*		p**	OR	CI (95%)
Genotype									
CC	57	81,43%	26	86,67%	0,52	CT vs CC	0,72	1,48	(0,40;4,695)
CT	13	18,57%	4	13,33%					
Allele									
C	127	90,71%	56	93,33%	0,54	T vs C	0,78	1,43	(0,41;4,31)
T	13	9,29%	4	6,67%					

We discovered that the distribution of CC-genotype dominates the heterozygosity. Among the patients the distribution of this particular genotype is 81,43% while in the control volunteers this percentage calculates 86,67%. The CT-genotype is discovered in 18,57% of the patients and in 13,33% of the healthy individuals. When comparing the allele distribution, we noticed that the C-allele has significant prevalence in both subgroups – 90,71% from the patients and 93,33% from the healthy controls are caring the C-allele, while only 9,29% from the patients and 6,67%from the control subgroup are positive for the T-allele.

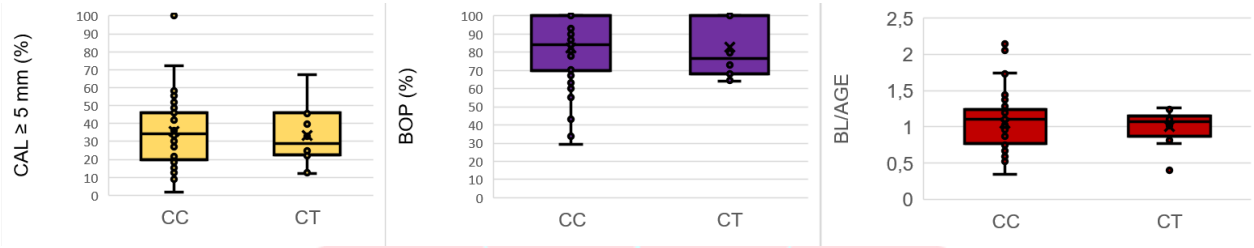

Figure 1. CAL ≥ 5 mm, BoP and Bl/Age – comparison between genotypes.

Results on several parameters of periodontitis will be presented. We compared the severe attachment loss (CAL ≥ 5 mm) among the patients with CC- and CT-genotypes.

The box-plot diagram demonstrates the wider range of values in the patients with CC-genotype with several extremely lower and higher values. Despite these results the values are comparable. Regarding to the BoP in both sub-groups the highest values measuring the distribution of the periodontal inflammation is reaching 100%, but the CT- genotype patients have lower level of the median which shows lower average level of the inflammation. The Bl/Age shows a comparable data according to the position of the median, but in the sub-group of CC-genotype patients both the highest and the lowest results are distributed. These result are interpreted according to the tobacco smoking which is a major modifying factor in the pathogenesis of periodontitis. Differences in some periodontal parameters between the patients with both dominant genotypes were found.

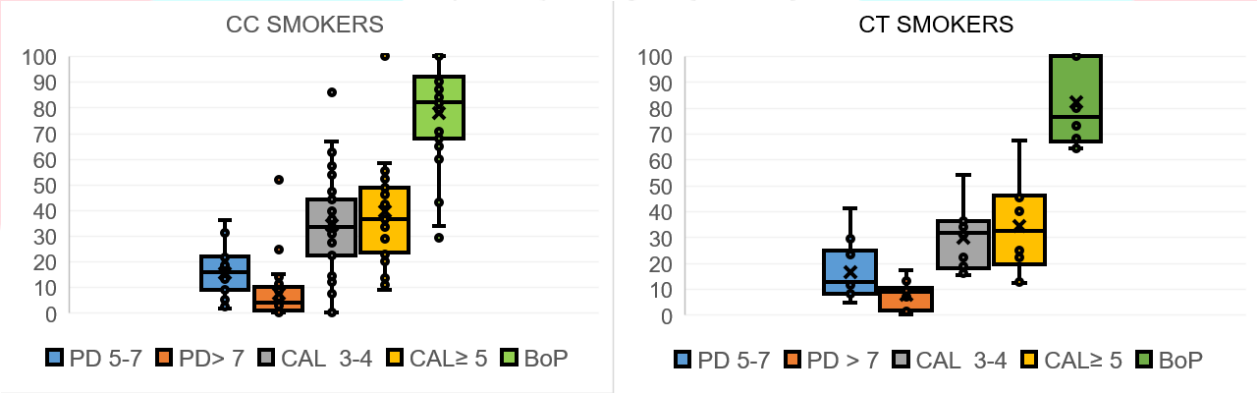

Figure 2. Periodontal parameters in smokers compared by genotypes.

In patients with the CC genotype, periodontal sites with a probing depth of 5-7 mm are less common, compared to the same parameter in the carriers of the CT genotype. The prevalence of periodontal pockets greater than 7 mm in depth was comparable in both subgroups, but some higher values in heterozygous patients were observed. Regarding CAL 3-4 mm values in a wider range were recorded in CC genotype, while for CAL ≥ 5 mm a wider range was recorded in CT genotype. In the case of BoP, higher values were found in the carriers of the CT genotype.

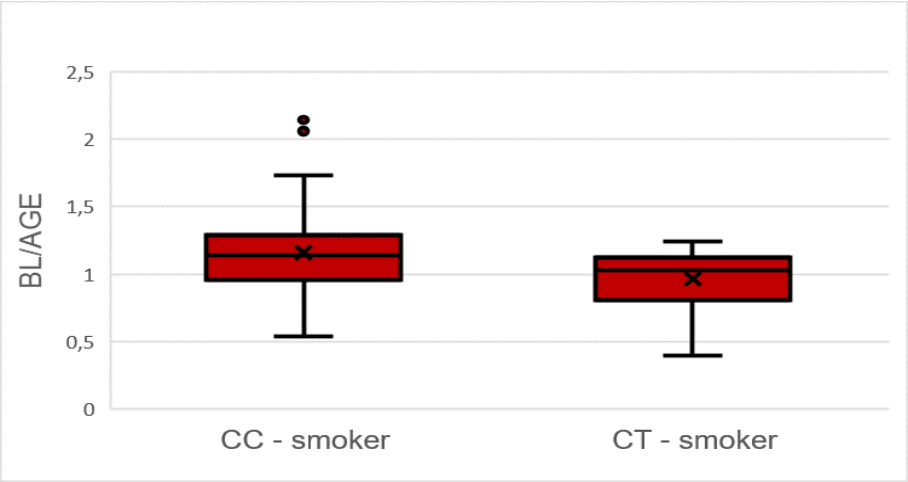

Figure 3. Bl/Age in smokers compared by genotypes.

When comparing the Bl/Age in patients - smokers, carriers of both genotypes - CC and CT, a higher value of the indicated coefficient is found in the homozygous patients. From the chart it can be seen that two of them demonstrate extremely high values. It is clear that the patients with CT genotype the BoP and CAL ≥ 5 mm is more pronounced compared to the other sub-group, whereas the Bl/Age has higher values in CC-genotype smokers.

Discussion

In a study of the Bulgarian population for SNP of IL-13 -1112, among 71 patients with periodontitis and 30 healthy controls, the presence of three genotypes was found - CC genotype, CT genotype and TT genotype, which is isolated in only one patient with severe periodontitis. Of the sub-group of the CC genotype participants, 68.7% have periodontitis, and 31.7% are healthy. In heterozygous individuals, 75% have periodontitis and 25% are healthy. Our data suggested that it can be assumed that patients with the CC genotype have a tendency to have a more severe course of periodontal disease, especially in terms of clinical attachment loss and bleeding on probing, representing disease activity. In the studied patients, a statistically significant difference was also found in relation to Bl/Age with a level of significance of $p < 0.1$ - in smokers this index is higher compared to non-smokers. The obtained result confirms the literature data about a more severe course of periodontitis in smokers.

The present study confirmed the results of other authors who, similar to us, tried to find evidence for the significance of the polymorphism of the interleukin 13 -1112 gene in relation to periodontitis and did not find statistically significant differences. Such results are shown by Gorgun et al., 2021, who studied 120 patients with periodontitis and 70 periodontally healthy individuals, and concluded that IL-13 -1112 gene polymorphism was not associated with periodontal diseases in their studied population. However, the same authors found that the levels of interleukin 13 gene expression in the gingival fluid 6 weeks after mechanical periodontal therapy (non-surgical treatment) increased statistically significantly compared to the levels from the initial database - before treatment (at $p<0.05$) [6]. In data from meta-analyses provided by Zhang et al. the association between IL-13 -1112 gene polymorphism and periodontitis severity is discussed. Despite

systematic clinical data, no significant in most models association between disease and polymorphism was found [16].

Xin Liu and Hui Li, 2022, who also found in their study that there was no association of interleukin 13 with the pathogenesis of periodontitis. They also, like other researchers, suggest a probable role of the cytokines they studied - IL-13 and IL-4, in protective tissue processes - by influencing osteoclastogenesis and the activity of Th2 cells [17-20].

In a study in a Japanese population for the IL-13 -1112 SNP, the presence of all three genotypes was also found, with the TT genotype occurring relatively more frequently, compared to our results. Komazaki et al. studied 53 patients with periodontitis and 52 healthy controls. They found that homozygosity for the C-allele occurs more often in healthy controls than in patients with periodontitis and heterozygosity is more common in patients with periodontitis. A significant difference with the population studied by us is found in terms of homozygosity for the T-allele. In our study, only one patient showed the TT genotype, while in the Japanese population 5.5% of patients with periodontitis and 7.7% of healthy subjects were carriers of this genotype [21].

A study in a Taiwanese population of the IL-13 -1112 polymorphism by Wu et al. found the presence of three genotypes, with T-allele homozygosity being the rarest. The research team concluded that the CC genotype was associated with severe periodontitis with a risk of rapid progression only in non-smokers [22].

Studies in a Romanian population conducted by Talvan et al. also found no relationship between periodontitis and single nucleotide polymorphism of the studied proinflammatory cytokine [23]. Gonzales et al. found in a German population the presence of TT-genotype in 17.2% of patients with periodontitis and in almost 10% of healthy – results contrasting to our study. At the same time, a high rate of heterozygosity was registered in the same population [24].

Conclusion

Our study revealed a novel data about the presence of IL-13 – 1112 SNP in Bulgarian population in relation to periodontal disease. Within the limitations of the study we found some differences in the clinical course of periodontitis in both subgroups. Larger studies are needed in order to establish significant differences between the individuals with different genotype profile.

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