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Porphyromonas gingivalis and non-alcoholic fatty liver disease as combined factors of periodontitis

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ABSTRACT

Purpose: This study is to determine the quantitative level of *Porphyromonas gingivalis* (*P. gingivalis*) in the periodontal pocket and its gingipain virulence factor in patients with non-alcoholic fatty liver disease (NAFLD).

Methods: Dental status, composition of *P. gingivalis*, and levels of gingipain and blood endotoxin were studied in patients with NAFLD and in a control group. The quantitative composition of *P. gingivalis* was determined by the real-time quantitative polymerase chain reaction method (qRT-PCR). Gingipain K concentration in oral fluid was determined by an immunoenzymatic method.

Results: The level of individual oral hygiene in the NAFLD patients was found to be unsatisfactory. Structurally, periodontal pathology was represented mainly by chronic grade B periodontitis. When analysing the correlation interaction, a positive dynamic was found between *P. gingivalis* and the presence of generalized periodontitis (GP) (r=0.652; p=0.000) and between gingipain and GP (r=0.510; p=0.006). The endotoxemia value correlated positively with the quantitative index of *P. gingivalis* (r=0.695; p=0.004), which is explained by the fact that periodontopathogen endotoxin (LPS), when entering the vascular bed, increases the systemic endotoxin level in general. Inflammation-causing cytokines and LPS in NAFLD contribute to the formation of an anaerobic environment in the periodontium that favours the quantitative growth of *P. gingivalis*.

Conclusion: The highest levels of *P. gingivalis* and gingipain were recorded in patients with NAFLD, which is consistent with a background of decreased periodontal adaptive capabilities. The *P. gingivalis*/gingipain correlation ratio can allow the dentist to monitor the treatment of periodontal patients.

KEYWORDS

Periodontitis, chronic inflammation, gingipain, periodontopathogen.

Introduction

According to Socransky's theory, specific bacteria belonging to the group of periodontopathogens play an important role in the initiation of inflammatory diseases of the periodontal tissues [1]. Although these microorganisms are diverse, including more than 30 strains, periodontopathogens are not a chaotic cluster in the oral cavity, but form specific microcolonies and complexes, and are classified according to their virulence and pathogenicity for periodontal tissues into the 1st and 2nd order subgroups [2-4].

The 1st order subgroup contains three periodontopathogens: *Porphyromonas gingivalis (P. gingivalis), Aggregatibacter actinomycetemcomitans* and *Tanerella forsythia*. These bacteria are the most pathogenic for the periodontium; they have powerful virulence factors and are always present in the locus of chronic periodontitis (CP) [5]. It should be noted that these microorganisms belong to the oral cavity resident microflora and are normally found in small quantities in the area of the gingival sulcus or in other folds of the mucous membrane and have a specific function of maintaining the necessary level of activity of the local immune status [6,7].

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The periodontium is constantly influenced by various exogenous pathogenic factors, and microorganisms are only one of them. The oral cavity microflora makes up one of the body's biotopes, formed 2-3 hours after birth, and therefore the periodontium, in relation to it, has certain adaptive and protective capabilities [8,9]. The integrity of the epithelial barrier, constant movement of gingival fluid, local immunity control, the necessary partial pressure of oxygen, and minimum amount of plaque, although concurrently influenced by several exogenous factors, preserve periodontal health [10].

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diseases of periodontal tissues associated with metabolic pathologies are attracting special attention, and one of them is non-alcoholic fatty liver disease (NAFLD) [11-13]. The presence of NAFLD in a dental patient act as an endogenous factor in reducing the adaptive capacity of the periodontium, and in initiating and maintaining the inflammatory process through the systemic circulation as a source of pro-inflammatory cytokines [14]. In addition, NAFLD contributes to increased blood levels of microbial endotoxins [15]. Thus, somatic disease facilitates increased activity of specific periodontopathogens, and the occurrence and development of pathological changes in the periodontium [16].

One of the main 1st order periodontopathogens is *P. gingivalis*, which has powerful virulence factors. It is an obligate anaerobe, and therefore a healthy periodontium is able to resist this representative of the oral cavity–resident microflora [17,18]. However, in NAFLD, the protective capabilities of the periodontium decline and quantitative and qualitative changes caused by *P. gingivalis* begin to occur, i.e., infectivity (increase and growth of microcolonies) and invasion (intratissue penetration). Hypoxia phenomena in the periodontium supported by NAFLD contribute to the growth of anaerobes [19].

P. gingivalis has special processes, called fimbriae, on the surface of its membrane, which ensure tight adhesion to the epithelial layer of the gums and have antigenic properties [20,21]. *P. gingivalis* has direct and indirect mechanisms of periodontal tissue destruction. By secreting special enzymes, i.e., gingipains, the bacterium destroys interepithelial contacts, and reduces the viscosity of the main substance of the connective tissue, and can therefore more easily invade [22,23]. Using various antigenic factors, the periodontopathogen attracts neutrophils with a wide spectrum of enzymatic activity, thus ensuring the mediated destruction of periodontal tissues.

The purpose of this study is to determine the quantitative level of *P. gingivalis* in the periodontal pocket and its gingipain virulence factor in patients with NAFLD.

Materials and methods

Ethical issues

The institutional ethics committee approved all studies. All participants enrolled in the study gave their informed consent and had an opportunity to withdraw from the study early.

Clinical issues

The study recruited patients with a verified NAFLD diagnosis and somatically healthy patients as from the control group. The median age [interquartile range] of the patients with NAFLD was 50 [42.00; 58.00] years. The two groups were matched in terms of gender and age. NAFLD diagnosis was established according to the national and international criteria (other factors linked to the development of secondary hepatic steatosis were excluded in all patients) [24-26]. To diagnose obesity and classify its degree, WHO criteria were used, based on the calculated body mass index (BMI). Dental examination was carried out according to the standard methods with the determination of the simplified oral hygiene index, the papillary-marginal-alveolar index, the papilla-bleeding index, the periodontal index (Russel), and the loss of attachment and the depth of gingival probing. The diagnosis of pathological periodontal changes was verified according to the classification of diseases and conditions of periodontal and peri-implant tissues (EFP & AAP World Workshop, 2018) [27].

The quantitative composition of *P. gingivalis* was determined by the real-time quantitative polymerase chain reaction method using universal primers. The material was collected from periodontal pockets using paper endodontic absorbers (AbsorbentPaperPoints by Maillefer, size #25). The absorbers were left in the pockets for 15-20 seconds with minimal contact with atmospheric air, and thereafter were immediately transferred to separate Eppendorf tubes with DNA-EXPRESS reagent, which is used for rapid lysis of biomass, and immediately sent to the laboratory. Four absorbers were used for each participant.

Gingipain K concentration in oral fluid was determined by an immunoenzymatic method using the HUMAN GINGIPAIN K (KGP) ELISA KIT (DRG Instruments GmbH, Germany), catalogue number MBS2800342, Lot#LO3UKG17. The concentration determination range is 15.6-2000.00 pg/ml; sensitivity:15.6 pg/ml.

Bacterial endotoxin concentration was determined in blood serum using an immunoenzymatic method and the LAL Chromogenic Endpoint Assay kit (Hycult Biotech, the Netherlands). The concentration determination range is from 0.01 to 10 units of ET/ml and the sensitivity is 0.01 unit of ET/ml. Blood was collected from the ulnar vein with minimal tourniquet in vacutainers with gel and coagulation activator to obtain serum and with K_3EDTA to obtain blood plasma.

Mathematical statistical methods

Statistical data processing was performed using the SPSS statistical package (version 17.0 for Windows; SPSS, Chicago, IL). The Kolmogorov-Smirnov test was used to test the sign for normality. Given the distribution of investigated characteristics, non-parametric methods were used to describe and compare indicators whose distribution differed from the normal one: calculation of the median and interquartile range of Me [Q1; Q3]; Mann-Whitney test. The comparison of qualitative features, as well as the study of the frequency of detection of indicators, was carried out using the $\chi 2$ criterion with analysis of conjugation tables. Correlations were evaluated using Pearson's correlation ratio for normally distributed quantitative traits, Spearman's coefficient for other types of distribution, and Kendall's coefficient for qualitative and quantitative indicators.

Results

A specific feature of the patients in the study group was the presence of excess weight, as confirmed by BMI, which exceeded the average acceptable value of the norm (Table I). The BMI of examined subjects in the control group was significantly lower than the upper limit and differed considerably from the average index of the main group (p=0.000).

Table I BMI value, (Me [Q1; Q3]).

INDEX	MAIN GROUP	CONTROL GROUP	*p*
BMI	32.2 [31.4; 37.4]	22.4 [20.45; 24.11]	0.000
BMI: body mass index			

We considered it important to obtain data on the level of systemic endotoxin (LPS) in the blood serum of the participants. Its quantitative level in the main group was higher than in somatically healthy subjects (Table II).

Table II Endotoxemia level in the two groups, (Me [Q1; Q3]).

INDEX	MAIN GROUP	CONTROL GROUP	*p*
LPS	0.9 [0.6; 1.08]	0.43 [0.12; 0.55]	0.000
LPS: systemic endotoxin			

First, after clinical examination, we've defined the presence of a periodontal inflammatory process in the subjects in both groups. The majority of patients with NAFLD (65.7%) were diagnosed with generalized periodontitis (GP). According to the level of severity of periodontal pathology, the typical clinical form was found to be stage I GP (40,7% of patients), while 26.7% had stage II GP, and 32.6% had no inflammatory periodontal pathology. In the control group, only one subject had stage I GP, while the others had a healthy periodontium (Figure 1). Clinical forms of GP were confirmed by hygiene and periodontal indices (Table III).

It should be noted that the level of individual oral hygiene in the main group was unsatisfactory because most of the patients did not practise regular dental hygiene, which is important for periodontal health. Regular oral hygiene is especially important in NAFLD subjects, since the adaptation of the periodontium to the direct action of exogenous factors decreases in this disease.

Figure 1 Clinical forms of periodontal diseases, %; Note: * is the level of statistical significance of differences versus the control group

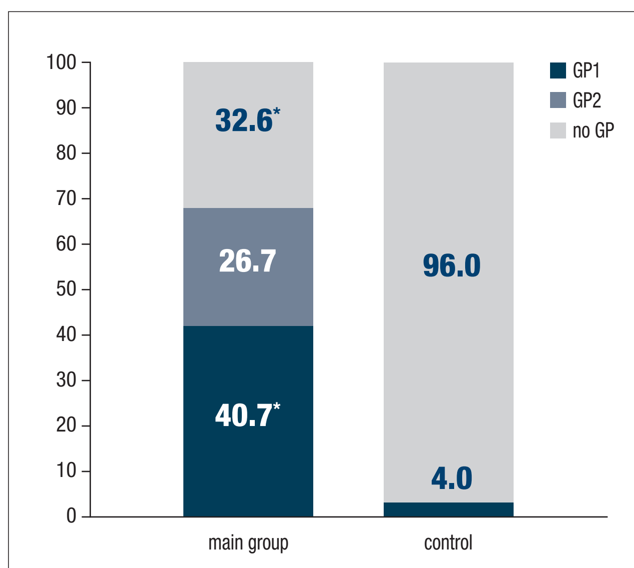

Table III Data from the physical examination of the periodontium in both groups (Me [Q1; Q3]).

INDEX	MAIN GROUP	CONTROL GROUP	*p*
OHI-S	2.3 [1.9; 2.6]	1.4 [1.1; 1.65]	0.000
PI	2.3 [1.6; 2.7]	0.3 [0.2; 0.85]	0.000
PMA	28 [25.0; 32.0]	9.0 [5.5; 13.0]	0.000
PBI	2.0 [1.0; 2.0]	0.28 [0.0; 1.0]	0.000
Loss of attachment, mm	3.5 [0.0; 4.0]	0.16 [0.0; 2.0]	0.000
Probing depth, mm	1.5 [1.0; 2.0]	2.0 [1.75; 2.55]	0.000
OHI-S: simplified oral hygiene index; **PI:** periodontal index; **PMA:** papillary-marginal-alveolar index; **PBI:** papilla-bleeding index			

The most frequent localization of periodontopathogens is the periodontal sulcus, and therefore the data regarding *P gingivalis* (Fig.2) were obtained in the two groups. The *P. gingivalis* quantitative index differed significantly between groups. Its highest level was recorded in patients with NAFLD, due to a decrease in both the adaptive capabilities of the periodontium and activity of the local immune system, as well as an unsatisfactory level of oral hygiene. The proteolytic enzyme gingipain, which is secreted only by *P. gingivalis*, had the highest values in the main group (Table IV).

When analysing the correlation interaction, a positive dynamic was found between *P. gingivalis* and the presence of GP (r=0.652; p=0.000) and between gingipain and GP (r=0.510; p=0.006). The endotoxemia value also positively correlated with the quantitative index of *P. gingivalis* (r=0.695; p=0.004),

Figure 2 *P. gingivalis* concentration in the subgingival area of gums; Note: * is the level of statistical significance of differences from control group.

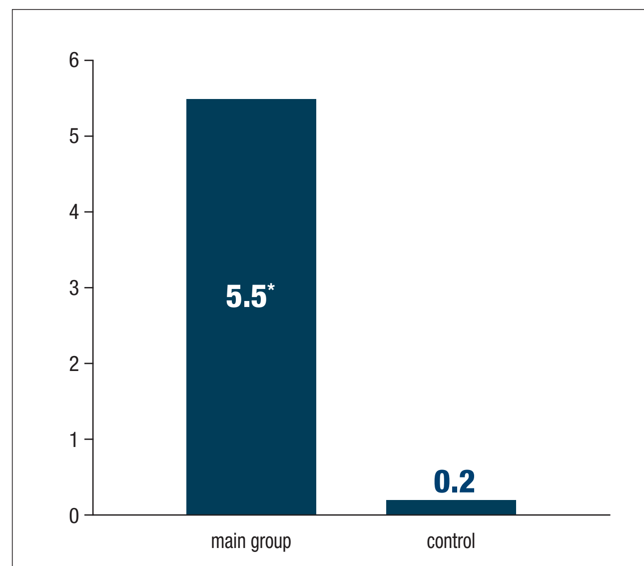

Table IV *P. gingivalis* virulence factor mean, (Me [Q1; Q3]).

INDEX	MAIN GROUP	CONTROL GROUP	*p*
Gingipain-K	98.9 [84.2; 125.6]	4.17 [2.85; 20.34]	0.001

which is explained by the fact that periodontopathogen LPS, when entering the vascular bed, increases the systemic endotoxin level in general.

We found a significantly positive correlations between *P. gingivalis* and PBI (r=0.457; p=0.002) and between *P. gingivalis* and probing depth (r=0.391; p=0.009). Indeed, an increase in the number of this periodontopathogen, a change in its phenotype and virulence, and the secretion of gingipain contributes to the onset of an inflammatory reaction in periodontal tissues, as well as vascular permeability, and therefore the PBI index increases. Conversely, when treating GP, a decreased PBI index facilitates the normalization of the *P. gingivalis* value and subsequent remission of the condition. It should be noted that a reduced depth of the gingival pocket when treating GP helps to eliminate a favourable anaerobic environment for the quantitative growth of *P. gingivalis* [28].

Discussion

The examined subjects in the control group had a BMI significantly lower than the upper limit and differed considerably from the average index recorded in the main group. On this basis, we identified excess fat tissue as a source of pro-inflammatory cytokines, and their possible entry into the periodontium through systemic blood circulation, as a risk factor for periodontitis [29]. The LPS level we measured characterizes a functional reduction of the physiological barriers that prevent long-term endotoxemia. In the human body, two of these barriers are particularly important, namely the intestinal microbiome and the liver. NAFLD directly affects this digestive organ, disrupting its detoxification properties, and dysbiosis in the composition of the intestinal microbiome, in general, is one of the etiological factors of the aforementioned somatic disease and of excess weight.

Endotoxemia is also one of the factors facilitating the initiation of inflammatory processes in the periodontium [30]. It is clear that a favourable background in the form of the aforementioned endogenous risk factors indirectly impairs the adaptive capabilities of the periodontium to interact directly with various exogenous factors and, especially, with specific microflora of the oral cavity [31].

It is possible that the absence of GP in some patients in the main group was associated with NAFLD duration (shorter), individual properties of periodontal tissues (a source of adaptation possibilities), the absence of harmful habits (smoking, etc.), and compliance with regular oral hygiene (brushing teeth twice a day).

As mentioned above, one aetiological factor of GP is the presence of specific microorganisms, i.e., periodontopathogens. Typically, these are permanent members of the microbial continuum of the oral cavity, but belong to the opportunistic microflora. In other words, initially they increase in number and growth of microcolonies occurs, which further contributes to qualitative changes and acquisition of a new phenotype with increased virulence in relation to periodontal tissues [32,33].

However, in our opinion, it is the control group that is of particular scientific interest. In one of the control group subjects, an inflammatory process in the periodontium was diagnosed, but there was no significant increase in the quantitative value of *P. gingivalis*. The quantitative indicator of gingipain, on the other hand, increased significantly, although it differed from that of the main group (p=0.001). This may mean that the change in the quantitative level of gingipain is a more sensitive and expressive marker of the onset of periodontopathogen activation; this hypothesis was confirmed by positive correlation between this proteolytic enzyme and *P. gingivalis* (r=0.534; p=0.003) [34,35].

However, it should be noted that *P. gingivalis*, which is an obligate anaerobe, can be detected only by a molecular genetic method, namely polymerase chain reaction. This method requires a specially equipped laboratory and appropriately trained personnel, and is therefore impossible to use at a regular dental appointment. The solution to this problem is to analyze correlations between a *P. gingivalis* quantitative indicator and dental indices such as periodontal papilla bleeding (PBI) and the probing depth of the periodontal sulcus. To do this, a dental mirror and a periodontal probe are the only instruments needed.

According to our study, gingipain showed a positive correlation with loss of epithelial attachment (r=0.379; p=0.0046). This is due to the fact that gingipain is a proteolytic enzyme that provides direct destruction of periodontal tissues, and also, having antigenic properties, attracts neutrophils to the locus of periodontal inflammation. To assess the real degree of destruction of periodontal tissues, data on the depth of probing of the periodontal pocket, on their own, are not enough. It is necessary also to consider recession of the gums, which generally gives a complete picture of the real loss of attachment. Table 3 shows that the control group subjects had a significantly deeper periodontal sulcus than the main group subjects. However, loss of epithelial attachment in somatically healthy individuals is practically absent, while in the main group it is significant and differs from control values [36,37].

Conclusions

NAFLD facilitates the onset of inflammatory processes in the periodontium due to the reduced capacity to resist the action of various exogenous factors, particularly the action of specific microorganisms, i.e., periodontopathogens.

Inflammation-causing cytokines and LPS in NAFLD contribute to the formation of an anaerobic environment in the periodontium (characterized primarily by high secretion of a specific proteolytic enzyme, gingipain) that favours the quantitative growth of *P. gingivalis*.

Gingipain level increases dramatically even in the absence of a reliable quantitative increase in *P. gingivalis*, and can be considered a sensitive marker in diagnosis and indicate a change in the phenotype of the periodontopathogen and an increase in its virulence.

By analysing and determining the *P. gingivalis*/gingipain correlation ratio with special indices available at a regular dental appointments, the dentist can monitor the dynamics of inflammation in GP patients and predict the onset and course of remission with subsequent stabilization.

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