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PARODONTALNO ZDRAVLJE I DETEKCIJA PARODONTALNIH BAKTERIJA KOD PACIJENATA SA AKUTNIM KORONARNIM SINDROMOM

PERIODONTAL HEALTH AND DETECTION OF PERIODONTAL BACTERIA IN PATIENTS WITH ACUTE CORONARY SYNDROME

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Sažetak

Uvod: *Nedavna istraživanja pokazuju da pacijenti sa parodontopatijom imaju veći rizik od nastanka kardiovaskularnih oboljenja od pacijenata bez parodontopatije. Novija istraživanja otkrila su da upala izazvana parodontopatijom značajno povećava rizik od akutnog koronarnog sindroma (AKS).*
Cilj: *Cilj ove studije bio je istražiti parodontalni status kod pacijenata sa akutnim koronarnim sindromom i proceniti povezanost različitih parodontalnih parametara sa ovim stanjem.*
Materijal i metode: *Prvu grupu činili su pacijenti sa AKS i parodontopatijom. Pacijenti su pregledani 3 dana nakon ishemije. Drugu grupu činili su pacijenti koji su imali samo parodontopatiju. Kontrolnu grupu činili su zdravi pojedinci. Parodontalni parametri mereni su i upoređivani na osnovu karakteristika demografije i procenjivani između grupa. Težina parodontopatije analizirana je u oba slučaja.*
Rezultati: *Analiza parodontalnih paremetara pokazala je da su srednje vrednosti veće kod pacijenata u prvoj i drugoj grupi u odnosu na treću, kontrolnu, grupu, ali značajno veće u grupi sa AKS. Nivoi markera zapaljenja bili su najviši u prvoj grupi, u poređenju sa drugom i kontrolnom grupom. Parodontalni patogeni bili su prisutniji kod pacijenata sa AKS nego kod pacijenata sa parodontopatijom, što ukazuje na ozbiljnu bolest kod ovih bolesnika.*
Zaključak: *Ova studija podržava povezanost parodontopatije i AKS. Teška forma parodontalnog oboljenja prisutna je kod ovih bolesnika, što ukazuje da ono može dalje uticati na razvoj AKS.*

Ključne reči: *akutni koronarni sindrom, parodontopatija, parodontopatogeni, parodontalni parametri, terapija*

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Abstract

Introduction: *Recent studies have found that patients with periodontitis have greater risk of incurring fatal cardiovascular disease than patients without periodontitis. Emerging research has identified inflammation caused by periodontitis as significantly increasing the risk for ACS.*
Aim: *The aim of this study was to investigate a periodontal status in the patients with ACS, and to assess the association of different periodontal parameters with ACS.*
Material and methods: *In the first group, patients both with ACS and periodontitis were enrolled as cases. Patients were examined 3 days after ischemia. The second group consisted of patients who had only periodontitis. The control group consisted of healthy individuals. Periodontal parameters were measured and matched on the basis of demographic characteristics and assessed between the groups. The severity of periodontitis in both cases was analyzed.*
Results: *Analysis of the periodontal parameters showed that median scores were higher in patients in the first and the second group compared to the third control group but significantly higher in group with ACS. Levels of inflammatory markers were highest in the first group, compared to the second group and the control group. Periodontal pathogens were more strongly present in patients with ACS than in the group with periodontitis, indicating that it was a serious illness in these patients.*
Conclusion: *This study supports an association between periodontitis and ACS. Severe periodontitis is present in this patients indicating that periodontitis can further act on the development of ACS.*

Key words: *acute coronary syndrome, periodontitis, periodontopathogens, periodontal parameters, therapy*

Uvod

Akutni koronarni sindrom (AKS) glavni je uzrok oboljevanja širom sveta[1]. Nekoliko studija sugeriše da je razvoj AKS povezan sa različitim vrstama oralnih infekcija[2,3], dok su drugi autori bili oprezniji[4,5]. Epidemiološke studije pokazale su povezanost parodontopatije i koronarnih bolesti[6,7]. Iz retrospektivnih analiza zaključeno je da bi parodontopatija mogla biti nezavisni faktor rizika za kardiovaskularne bolesti i ishemijski moždani udar[8,9]. Iako su faktori kao što su pušenje, hiper-holesterolemija, gojaznost, hipertenzija i dijabetes dobro utvrđeni faktori rizika za AKS, rezultati ispitivanja ukazuju na to da parodontalno oboljenje može biti povezano i sa AKS, jer su ovi faktori prisutni kod pacijenata sa parodontopatijom.

Parodontopatija je rezultat složene interakcije između hronične bakterijske infekcije i lokalnog i sistemskog inflamatornog odgovora domaćina[10]. Hipoteza je da hronični zapaljenjski teret parodontopatije, kao i odgovor domaćina na ovu upalu, mogu biti uključeni u razvoj kardiovaskularne bolesti[11].

Infarkt miokarda i dentalne infekcije su česte, ali njihov odnos nije dovoljno istražen u srpskoj populaciji. Čini se da parodontalni indeksi pokazuju jaču povezanost, što ukazuje na to da parodontopatija može biti opšti pokazatelj ličnog zdravlja i može uzročno biti povezana sa rizikom od nastanka AKS. Literarni rezultati pokazuju da markeri akutnog zapaljenja i hronične infektivne bolesti mogu povećati rizik od nastanka AKS[12]. Pored toga, prisustvo parodontalnih patogena povezano je sa povišenim markerima zapaljenja i AKS[13,6].

Cilj ove studije bio je da se ispita: I) da li je akutni koronarni sindrom povezan sa tipom i težinom parodontalnog oboljenja kod pacijenata sa prvom epizodom AKS; II) da li parodontalni inflamatorni procesi doprinose riziku od infarkta miokarda i; III) prisustvo parodontalnih patogena (*Porphyromonas-gingivalis – P.g. i Aggregatebacter actinomycetemcomitans – A.a.*) u parodontalnim džepovima pacijenata sa akutnim koronarnim sindromom u srpskoj populaciji u Nišu.

Materijal i metode

Ova studija obuhvatila je 250 učesnika. Svi pacijenti dali su informativni i potpisani pristanak za učešće u studiji. Studiju je pregledao i odobrio Etički odbor Medicinskog fakulteta u Nišu (br: 01-2800-5).

Introduction

Acute coronary syndrome (ACS) is a major cause of morbidity worldwide 1. Several studies have suggested that development of ACS is related to various types of oral infections[2,3], whereas others have been more cautious[4,5]. Epidemiological studies have shown an association between periodontitis and coronary heart disease[6,7].

It was, therefore, concluded from retrospective analysis that periodontitis could be an independent risk factor for cardiovascular disease and ischemic stroke[8,9]. While the factors such as smoking, hypercholesterolemia, obesity, hypertension, and diabetes are well-established risk factors for ACS, studies results suggest that periodontal disease may also be associated with ACS since these factors are present in patients with periodontitis.

Periodontitis results from a complex interplay between chronic bacterial infection and the local and systemic inflammatory host response[10]. It has been hypothesized that the chronic inflammatory burden of periodontal disease and the host response to this inflammation may be involved in the development of cardiovascular disease[11].

Myocardial infarction and dental infections are common, but their relationship is not sufficiently investigated in the Serbian population. The periodontal index seemed to have stronger association, indicating that periodontitis may be general indicator of personal health and may causally related to ACS risk. Markers of acute inflammation and chronic infectious diseases were discussed to increase the risk of ACS[12]. In addition, the presence of periodontal pathogens has been associated with elevated inflammatory markers and ACS[13,6].

The aim of this case-control study was to investigate: i) whether acute coronary syndrome was related to the type and severity of periodontitis in patients with a first episode of ACS, ii) whether periodontal inflammatory processes contribute to the risk of myocardial infarction and iii) the presence of periodontal pathogens (*Porphyromonas gingivalis-P.g. and Agreggatebacter actinomycetemcomitans-A.a.*) in periodontal pockets of patients with acute coronary syndrome in Serbian population in Niš.

Material and Methodology

This study included 250 participants. All patients gave informed and signed consent for study participation. The study

U prvoj grupi bilo je 100 bolesnika sa AKS i parodontopatijom. Pacijenti ove grupe hospitalizovani su na Odeljenju za kardiologiju Kliničkog centra u Nišu, sa prvom epizodom simptoma akutnog infarkta miokarda. Pacijenti su odabrani na osnovu potvrđene dijagnoze infarkta miokarda. Sve ispitanike klinički je pregledao kardiolog. Parodontološki status (klinički parodontalni parametri i prisustvo parodontopatija) ispitivan je 3 dana nakon ishemije, od strane jednog parodontologa.

U drugoj grupi, 100 pacijenata sa parodontopatijom, koji nisu imali istoriju bilo koje srčane bolesti, birano je u Službi za parodontologiju i oralnu medicinu Klinike za stomatologiju Medicinskog fakulteta u Nišu. Ispitanici sa teškom generalizovanom parodontopatijom bili su pozvani da učestvuju u studiji. Sve učesnike pregledao je jedan parodontolog.

Treća grupa (kontrolna grupa) sastojala se od 50 ispitanika, za koje je utvrđeno da nemaju kliničke nalaze AKS i parodontopatije.

Kriterijumi za isključenje pacijenata iz studije bili su trudnoća, nemogućnost davanja saglasnosti ili saradnje pri stomatološkom pregledu u roku od jedne nedelje nakon ishemije, bilo koje poznato stanje u kome je potreban profilaktički antibiotski tretman pre stomatološkog pregleda i istorija i/ili prisustvo drugih infekcija. Prvu posetu pacijentima obavio je kalibrirani ispitivač koji je prikupio kompletnu anamnezu i standardne kliničke parodontalne parametre.

Parodontalna infekcija dijagnostikovana je na osnovu kliničkog pregleda parodontalnih parametara. Umerena parodontopatija dijagnostikovana je onda kada je dubina parodontalnog džepa (DPDž) između 4 mm i 5 mm, a gubitak nivoa epitelnog pripoja (NEP) do 3 mm. Teška parodontopatija dijagnostikovana je onda kada je parodontalni džep bio 5 mm ili više, a gubitak nivoa epitelnog pripoja 3 mm ili veći[14]. Ovi nivoi težine parodontalnog oboljenja izabrani su kako bi povećali verovatnoću otkrivanja sistemskog opterećenja usled lokalne parodontalne infekcije. Za procenu parodontopatije, kao varijable izabrani su NEP, DPDž, inflamacija gingive (GI), krvarenje pri sondiranju (Ikrv) i indeks plaka (PlI). Parodontalno ispitivanje izvedeno je na četiri mesta na svakom zubu (bukalno, mezijalno, lingvalno (palatinalno) i distalno). Srednje vrednosti pojedinačno su izračunavane. Nivoi pripoja analizirani su kao kontinuirana promenljiva (≤ 3 mm).

had been reviewed and approved by the Scientific Ethical Committee of the Faculty of Medicine in Niš (No: 01-2800-5).

In the first group, there were 100 patients with ACS and periodontitis. They were obtained from patients hospitalized to Department of Cardiology, Faculty of Medicine in Niš, with a first episode of symptoms of acute myocardial infarction. The patients were selected on the basis of confirmed diagnosis of myocardial infarction. All subjects were clinically examined by a cardiologist. Patient's periodontal status (clinical periodontal parameters and presence of periodontopathogens) was examined 3 days after ischemia by one periodontologist.

In the second group, 100 patients with periodontitis were recruited from subjects referred to the Department of Periodontology of the Dental Clinic, Faculty of Medicine, but who had no history of any heart disease. Subjects presenting with severe generalized periodontitis were invited to participate in the study. All participants were examined by periodontologist.

The third group (control group) consisted of 50 subjects who were found free from clinical evidence of ACS and periodontitis.

Exclusion criteria for patients from study were pregnancy, inability to give informed consent or to cooperate in the dental examination within 1 week after ischemia, any known condition in which a prophylactic antibiotic treatment before dental examination was required, and history and/or presence of other infections. A baseline visit was conducted by a calibrated examiner who collected a complete medical history and standard clinical periodontal parameters.

Periodontal infection was diagnosed on the basis of clinical examination of periodontal parameters. Moderate periodontitis was diagnosed if periodontal pocket depth (PPD) was between 4 and 5 mm and clinical attachment loss - CAL to 3 mm. Severe periodontitis was diagnosed if periodontal pocket was 5 mm or more, with clinical attachment loss of 3 mm or greater[14].

These levels of periodontitis severity were chosen to increase probability of detection of a systemic burden from the local periodontal infection. For assessment of periodontitis, the CAL, PPD, gingival inflammation (GI), bleeding on probing (BOP) and plaque index (PI) were selected as the variables. Periodontal probe performed at four sites in each tooth (buccal, mesio-lingual, lingual and disto-lingual). Mean values were individually calculated.

Inflamacija gingive i gingivalno krvarenje određivani su Löe-Silnessovim gingivalnim indeksom[15]. Oralna higijena (PlI) procenjivana je Sillness-Löeovim indeksom plaka[15]. Srednje vrednosti pojedinačno su izračunavane.

Sve osobe pregledane su pomoću veštačkog svetla i stomatološkog ogledalca. Sve stomatološke preglede obavio je jedan parodontolog. Nakon određenog parodontalnog statusa, ispitanici su kategorisani prema najgorem parodontalnom stanju u ustima.

Anketirani su svi pojedinci korišćenjem standardizovanog upitnika, koji je bio fokusiran na prethodne bolesti i faktore rizika. Kovarijabilni elementi uključivali su sociodemografske promenljive i utvrđene faktore rizika za kardiovaskularne bolesti (starost, pol, obrazovanje, status pušenja, istorija dijabetesa i indeks telesne mase).

Uzorci subgingivalnog plaka sakupljeni su na početku studije iz najdubljih džepova, po jedan u svakom kvadrantu. Laboratorijska faza uključivala je analizu uzoraka korišćenjem višestrukih PCR metoda, koje uključuju istovremeno amplifikacione sekvence DNK obe bakterijske vrste (*P.g., A.a.*). Uzorci su pripremljeni pre PCR analize, a zatim su davani u odgovarajućoj količini u reakcionoj smeši. Reakciona smeša je korišćena sa zapreminom od 25 µl, koja se sastoji od PCR/Mg++ pufera, 1,5 µl svakog prajmera, 1U Taq DNK polimeraze i 3 µl supernatanta DNK. PCR je izveden na Thermo Hybaid aparatu (Thermo, Valtham, MA), programiranom na unapred definisane parametre. Posle pojačanja, usledila je elektroforeza sa 8% gela poliakril-amida. Pojačani fragmenti vizuelizovani su na ultraljubičastom transiluminatoru, nakon bojenja etijum-bromidom (Slika 1)[33].

Attachment levels were analyzed as continuous variable (≤3 mm). Gingival inflammation and gingival bleeding were determined by the Löe and Silness gingival index[15].

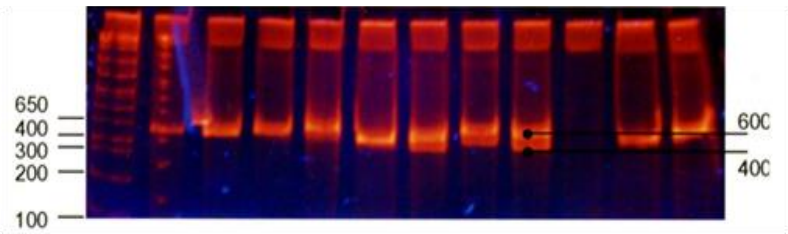
Oral hygiene (PI) was assessed by the Sillness and Löe plaque index[15]. Mean values were individually calculated.

All individuals were examined using a standard dental light and a dental mirror. All dental examinations were performed by one periodontologist. For periodontal status, subjects were categorized according to the worst periodontal condition in the mouth.

All individuals were interviewed by trained interviewers using a standardized questionnaire that focused on previous diseases, and risk factors. The covariables included sociodemographic variables and established risk factors for cardiovascular disease (age, sex, education, smoking status, history of diabetes, and body mass index).

Samples of subgingival periodontal plaque were collected at baseline from the deepest pockets, one in each quadrant. Laboratory phase included the analysis of samples using multiple PCR method, which involved the simultaneous amplification DNA sequences of both bacterial species (*P.g., A.a.*). Samples were prepared before PCR analysis, and subsequently administrated in appropriate amount in the reaction mixture. Reaction mixture was used with volume of 25 µl consisting of PCR/Mg++ buffer, 1.5 µl of each primer, 1U Taq DNA polymerase and 3 µl of DNA supernatant. PCR was carried out on ThermoHybaid apparatus (Thermo, Waltham, MA.) programmed to pre-defined parameters. After amplification electrophoresis was followed at 8% polyacrile-amide gel. Amplified fragments were visualized on the ultraviolet transilluminator, after staining with ethidium bromide (Fig. 1)[33].

Slika. 1. Amplificirani fragmenti *P.gingivalis* (400bp) i *A.actinomycetemcomitans* (600bp)[33]
Fig.1. Amplified fragments of *P.gingivalis* (400bp) and *A.actinomycetemcomitans* (600bp)[33]



Statistička analiza

Rezultati su izraženi kao srednja vrednost ± standardna greška srednje vrednosti u svakoj grupi. Višestruka poređenja izvršena su korišćenjem ANOVA. Vilijamov test korišćen je za post hoc poređenja. Vrednost verovatnoće p<0,05 smatrana je statistički značajnom.

Results were expressed as mean±standard error of the mean in each group. Multiple comparisons were performed by ANOVA. Williams' test was used for post-hoc comparisons. A probability value p<0.05 was considered statistically significant.

Tabela 1. Polna i starosna struktura ispitanika
Table 1. Gender and age distribution of respondents

Varijable/variable	I (ACS + PD)	II (PD)	III (Control group)	p- value
Pol/Gender (n°,%)				
muški/male	64 (64%)^{c**}	54 (54 %)^{c*}	14 (28 %)	χ^2 = 8.715
ženski/female	36 (36%)	46 (46%)	36 (72%)	p < 0.05
Godine / Age				ANOVA
SV ± SD / Mean ± SD	56.94 ± 13.42^{b**c***}	48.76 ± 15.83	42.80 ± 5.76	F = 9.789 p < 0.001

b–vs II, c–vs III
*–p<0,05; **–p<0,01; **–p<0,001

Tabela 2. Osnovne karakteristike tretirane populacije sa AKS + PD, PD i kontrola
Table 2. The basic characteristics of the treated population with ACS+PD, PD and control

Varijabile/Variable	I(AKS+PD) (ACS+PD)	II (PD) (PD)	III (Kontrolna grupa) (Control group)	p -value
Edukacija / Education (n°, %)				
Srednja škola / High school	58 (58%)^{c*}	64 (64%)^{c**}	16 (32 %)	χ^2 = 7.166 p
Fakultet/Faculty	42 (42%)	36 (36%)	34(68 %)	< 0.05
Socijalni status / Social status (n°, %)				
Loš/Bad	72 (72%)^{c***}	66 (66%)^{c**}	14 (32%)	χ^2 = 14.48 p
Dobar/Good	28 (28%)	34 (34%)	36 (68%)	< 0.001
Pušenje/Smoking (n°, %)				
Da/Yes	46 (46%)	38 (38%)	20 (40%)	χ^2 = 0.692
Ne/No	54 (54%)	62 (62%)	30 (60%)	n.s.
Fizička aktivnost / Phisycal activty (n°, %)				
Aktivan/Active	10 (10%)	30 (30%)	12 (24%)	χ^2 = 6.26 p <
Pasivan/Passive	90 (90%)^{b*}	70 (70%)	38 (76%)	0,05
Upotreba lekova / Drug use (n°, %)				
Da/Yes	100 (100%)^{b,c***}	26 (26%)	6 (12%)	χ^2 = 75.81 p
Ne/No	0 (%)	74 (74%)	44 (88%)	< 0.001
Dijabetes / Diabetes, (n°, %)				
Da/Yes	38 (38%)^{b**c***}	14 (14%)	0	χ^2 = 16.948
Ne/No	62 (62%)	86 (86%)	50 (100%)	p < 0.001
Hipertenzija / Hipertension, (n°, %)				
Da/Yes	68 (68%)^{bc***}	32(32%)^{c**}68	0	χ^2 = 34.333
Ne/No	32 (32%)	(68%)	50 (100%)	p < 0.001

b–vs II, c–vs III
*–p<0,05; **–p<0,01; ***–p<0,001; n.s.-no significant (nesignifikantno)

Rezultati

Karakteristike istraživačke populacije prikazane su u tabelama 1 i 2.

S obzirom na pol i starost pacijenata u obe grupe, parodontopatija i AKS češći su kod muškaraca i starijih osoba. Inače, dobro je poznata povezanost ovih bolesti sa godinama i polom.

Nivo obrazovanja kod većine pacijenata bio je nizak (<12 godina). Parodontalni pacijenti i pacijenti sa AKS+PD nalaze se u grupi nižeg obrazovanja u poređenju sa osobama koje su zdrave (42% i 36% u odnosu na 68%) (p<0,05).

Socijalni status bolesnika iz obe grupe bio je loš (72% i 66%) u poređenju sa kontrolnom grupom (32%). Postoji statistički značajna razlika među grupama (p<0,001).

Pušači u prvoj grupi su bili (46%), u drugoj grupi (38%), a u kontrolnoj grupi 20 (40%). Pušači su češći u eksperimentaloj grupi u poređenju sa kontrolnom grupom, ali nema značajne razlike. Pušenje je inače faktor rizika za obe bolesti.

Fizičku aktivnost ne praktikuje većina ispitanika, u obe eksperimentalne grupe. U prvoj grupi aktivno je samo 10, a u drugoj grupi samo 30 ispitanika (30%). U kontrolnoj grupi je12 aktivnih pacijenata. U PD grupi bili su, statistički dominantno, neaktivni ispitanici (p<0,05), a njihov broj bio je zastupljeniji u grupi AKS+PD (p<0,001). Pacijenti sa AKS rade manje vežbi od ljudi iz drugih grupa. Poznato je da su redovne fizičke aktivnosti povezane sa nižim rizikom od nastanka AKS.

Upotreba lekova primećena je kod svih bolesnika sa AKS+PD (100%), dok manji procenat pacijenata upotrebljava lekove u grupi sa PD (26%). U kontrolnoj grupi samo 12% ljudi koristi bilo koji lek, ali samo kada im je potreban. Grupe se statistički razlikuju u odnosu na upotrebu lekova (p<0,001).

Dijabetes je imalo samo 14 pacijenata od ukupnog broja pacijenata sa parodontopatijom, dok je 38 pacijenata bilo sa dijabetesom u grupi sa AKS+PD. U kontrolnoj grupi nije bilo pacijenata sa dijabetesom. Razlike u postojanju dijabetesa u ovoj studiji odgovaraju činjenici da je dijabetes poznat faktor rizika za nastanak kardiovaskularnog i parodontalnog oboljenja (p<0,001).

Hipertenzija u grupi sa PD zastupljena je u svega 32% pacijenata, dok je u AKS grupi taj procenat 68.

Results

Characteristics of the study population shown in Table 1 and 2.

In terms of gender and age in both groups of diseases, periodontitis and ACS were more common men and the elderly. Otherwise it is well known connection compared to the year and a gender for both diseases.

Level of education was low (<12 years) in most subjects. Periodontal patients and patients with ACS+PD were in the group with lower education compared to the healthy-control persons (42%, 36% vs. 68%) (p<0.05).

Social status in both groups of patients was poor (72% and 66%) compared to the control group (32%). There is a statistically significant difference among the groups (p<0.001).

Smokers in the first group made up 46%, in the second group 38%, and in the control group there were 20 (40%) of them. Smokers were more common among patients of the experimental group compared to the healthy group, but there was no significant difference. Smoking is otherwise a risk factor for both diseases.

Physical activity was not practiced by the majority of respondents in both experimental groups. In the first group, only 10 patients and in the other group only 30 patients (30%) were active. In the control group there were 12 active patients. In the PD group, there were statistically predominant inactive subjects (p<0.05), and even more dominant in the group ACS+PD (p<0.001). Patients with ACS did less exercise than people in other groups. It is known that regular physical activity goes along with a lower risk for ACS.

The use of drugs was observed in all patients with ACS+PD (100%), while a smaller percentage (26%) in individuals with only PD. In the control group only 12% of people were using any medications, but only when they needed them. Groups were statistically different in relation to the use of drugs (p<0.001).

Diabetes had only 14 of the total number of patients with periodontitis, while 38 patients were with diabetes in the group with ACS+PD. In the control group, there were no patients with diabetes. Differences in the existence of diabetes in this study correspond to the fact that diabetes is a known risk factor for cardiovascular and periodontal disease (p<0.001).

Pacijenti u kontrolnoj grupi bili su bez hipertenzije. U grupi sa AKS+PD bilo je statistički više pacijenata sa hipertenzijom u poređenju sa ispitanicima PD grupe (p<0,001). Grupe se značajno razlikuju u pogledu prisustva hipertenzije (p<0,001).

Teška forma parodontopatije bila je značajno više zastupljena kod pacijenata u grupi sa AKS nego kod pacijenata PD grupe (Tabela 3.)

Hypertension among the patients with PD was present in only 32%, and in 68% inthe ACS group. Peoplein the controlgroup were without hypertension. In the ACS+PD group, there were statistically more patients withhypertensioncompared tosubjectswith PD (p<0.001). Groups were significantly differentinterms ofpresenceof hypertension (p<0.001).

Severe periodontitis were significantly greater for cases in group with ACS than for cases with periodontitis (Table 3.)

Tabela 3. Parodontalni indeksi u svim grupama pacijenata
Table 3.Periodontal findings in all groups of patients

Varijabile / Variable	I (AKS + PD) (ACS + PD)	II (PD) (PD)	III (Kontrolna grupa) (Control group)	ANOVA p-value
PlI/PlI	1.90 ± 0.58 ^{c***}	1.64 ±0 .53 ^{c***}	0.52 ± 0.42	F = 58.650 p < 0.001
Ikrv/BOP	1.70 ± 0.46 ^{c***}	1.72 ± 0.45 ^{c***}	0.40 ± 0.38	F = 86.971 p < 0.001
GI/GI	1.76 ± 0.43 ^{c***}	1.76 ± 0.43 ^{c***}	0.40 ± 0.38	F = 103.795 p < 0.001
DPDž mm / PPD, mm mean±SD	5.14 ± 1.04 ^{bc***}	4.68 ± 1.11 ^{c***}	1.90 ± 0.55	F = 94.454 p < 0.001
<5mm	52 (52%)	66 (66%)	50 (100%)	χ^2 = 17.48
≥5mm	48 (48%) ^{c***}	34 (34%) ^{c***}		p < 0.001
CAL, mm	6.28 ± 1.04 ^{bc***}	5.72 ± 0.96 ^{c***}	1.90 ± 0.55	F = 198.557 p < 0.001

b–vs I, c–vs III
*–p<0,05; **–p<0,01; ***–p<0,001; n.s.-no significant
Footnotes: **PI**-plaque index; **BOP**-bleeding on probing:**GI**-gingival index
PPD-periodontal pocket depth; **CAL**-clinical attachment loss

Prevalencija parodontopatije i parodontalnih indeksa bila je veća kod osoba sa AKS+PD u poređenju sa pacijentima drugih grupa (p<0,001). Parodontalni parametri upoređivani su u odnosu na srednje vrednosti između ispitivnih grupa i kontrolne grupe. Pacijenti sa AKS imaju veću količinu dentalnog plaka, dublje parodontalne džepove i veći gubitak nivoa pripojnog epitela (p<0,001).

Mikrobiološka analiza pokazala je prisustvo *P.g.* u 76% slučajeva i *A.a.* u 32% slučajeva u grupi sa AKS+PD, 34% *P.g.* i 16% *A.a.* u grupi sa PD. U kontrolnoj grupi *P.g.* bio je prisutan u 4% slučajeva, dok *A.a.* nije bio prisutan. Prisustvo *Porphyromonas gingivalis* (p<0,001) i *Aggregatibacter actino-mycetemcomitans* (p<0,01) značajno se razlikovalo i bilo je značajno veće u grupama sa AKS+PD i PD nego u kontrolnoj grupi (p<0,001).

Prevalence of periodontitis and periodontal indicators were higher in those with ACS+PD compared with other groups (p<0.001). Periodontal parameters were compared in terms of median values between cases and controls.Patients with ACS had a greater amount of bacterial plaque, deeper periodontal pockets, and greater loss of epithelial attachment (p<0.001).

Microbial analysis showed the presence of P.g. in 76% and A.a. in 32% in the group with ACS+PD, and 34% of P.g. and 16% of A.a. in the group with PD. In the control group, P.g. was present in 4% cases, while A.a. was not present. Presence of *Porphyromonas gingivalis (p<0.001), and Aggregatibacter actinomycetemcomitans* (p<0.01) were significantly different and significantly higher in groups with ACS+PD and PD than in controls (p<0.001).

Diskusija

Rezultati ove studije pokazali su značajnu povezanost lošeg parodontalnog statusa i AKS, korišćenjem parodontalnih indeksa. Podaci pokazuju da su parodontalni parametri bili povezivani sa srčanim udarima kod osoba starih 40 i više godina (Tab.1).

Podaci su pokazali da loše zdravlje zuba i, posebno, parodontopatija povećavaju rizik od pojave AKS, pružajući dokaze da dentalne infekcije imaju niz rizičnih faktora zajedničkih sa AKS. Ova veza pažljivo je kontrolisana za niz kardiovaskularnih faktora rizika kao kovarijanata, uključujući starost, muški pol, pušenje cigareta, dijabetes melitus, gojaznost, hipertenziju, fizičku neaktivnost, socijalni status i obrazovanje, a podaci su u saglasnosti s drugim studijama, koje su pokazale pozitivnu povezanost parodontopatije i rizika od kardiovaskularnih bolesti[16]. Mnogi faktori rizika za nastanak AKS bili su prisutni kod pacijenata sa parodontopatijom (Tab.2).

Parodontalno oboljenje započinje mikrobnom infekcijom. Akumulacije na zubima neophodne su za pokretanje i napredovanje parodontopatije. Kada se bakterijski biofilm na zubima ne uklanja, ekološke promene dovode do pojave određenih bakterijskih vrsta, uključujući *P.g.* i *A.a.*, koji su povezani sa parodontopatijom. Ove bakterije, sa faktorima okoline i genetskim faktorima, ubrzavaju upalne procese u parodontu. Zapaljenje se pojavljuje kao interterativni AKS faktor. Međutim, zabeleženo je da se stepen zapaljenja povećava sa težinom parodontopatije i površinom inficiranog parodontalnog tkiva[17,18].

Parodontopatija, koja se obično javlja kod pacijenata sa AKS, takođe može poslužiti kao kofaktor. U istraživanju je pronađeno da se veća parodontalna infekcija i loše oralno zdravlje javljaju kod pacijenata sa AKS, u odnosu na pacijente samo sa parodontopatijom i u odnosu na kontrolne ispitanike (Tab. 3). Izgleda da su parodontalne infekcije značajno češće i teže među ispitanicima nego među kontrolama, što je u skladu sa ranijom studijom[8].

Sa svakom povišenom kategorijom parodontalnih parametara, rizik od srčanog udara se povećava.

Među osobama sa srčanim udarom bilo je mnogo više ispitanika koji su imali tešku formu parodontopatije od onih koji su imali samo parodontopatiju.

Discussion

The results of the present study showed a significant association between poor periodontal status and ACS regardless of the periodontal index used. The periodontal parameters were associated with a history of heart attack among persons aged 40years and over (Tab. 1).

Data have shown that poor dental health and, in particular, periodontitis increased the risk of occurrence of ACS, providing evidence that dental disease have a number of risk factors in common with ACS. The reported association was carefully controlled for a series of cardiovascular risk factors as confounders, including age, male gender, cigarette smoking, diabetes mellitus, obesity, hypertension, physical inactivity, social status and education, and the data are in agreement with other studies that have shown a positive association between periodontitis and the risk of cardiovascular disease events [16]. Many risk factors for ACS were presents in the patients with periodontitis (Tab. 2).

Periodontitis begins with a microbial infection. Bacterial accumulations on the teeth are essential to the initiation and progression of periodontitis. When bacterial biofilms on the teeth are not disrupted, ecologic changes lead to the bacterial species, including *P.g.* and *A.a.* which are associated with periodontitis. These bacteria with environmental and genetic factors accelerate inflammatory processes in periodontitis. Inflammation has emerged as an interactive ACS factor. It has been reported though, that the degree of inflammation increases with severity of periodontitis and area of infected periodontal tissue [17,18].

Periodontitis, commonly found in patients with ACS may also serve as a confounder. We found greater evidence of periodontal infection and poor dental health among patients with ACS than among patients with periodontitis and controls (Table 3). Periodontal infections seemed significantly more frequent and more severe among cases than among controls, in agreement with earlier study [8]. With each higher category of periodontal parameters, a history of heart attack increased. Among persons with a heart attack, there were much more subjects who had more severe periodontitis than those who had only

To bi se moglo odraziti na razlike u dizajnu studije i merama srčanih bolesti i parodontalnog oboljenja.

Primenom parodontalnih indeksa i parodontalnih patogena, pokazana je značajna povezanost lošeg parodontalnog statusa i AKS. Postojeće studije pružaju dokaze po kojima bi parodontalni indeksi najbolje opisali povezanost infekcije tkiva parodonta i ishemijskog udara. Štaviše, nijedna od većih studija nije proučavala parodontalnu infekciju u trenutku ishemijskog događaja.

Svi parodontalni parametri bili su značajno viši kod pacijenata sa AKS. Prema otkrićima u ovoj studiji, povišeni parodontalni indeksi mogu se smatrati nezavisnim faktorima rizika za razvoj kardiovaskularne bolesti. To je u skladu sa prethodnom studijom, koja je prijavila veći nivo inflamatornih markera kod pacijenata sa teškom parodontopatijom. Inflamacija je prepoznata kao značajan aktivni učesnik, kao i faktor rizika za razvoj mnogih hroničnih bolesti, uključujući aterosklerozu i kardiovaskularna oboljenja i parodontopatiju[19,20,21].

U ovom istraživanju pokazano je da su parodontopatogeni (*A.a, P.g.*) prisutni u velikom porastu kod pacijenata sa AKS, mnogo više nego kod pacijenata samo sa parodontopatijom. Rezultati su pokazali da ti parodontopatogeni mogu biti faktori rizika za budući AKS događaj, jer je veći porast parodontopatije praćen inflamatornom reakcijom tkiva parodonta. Međutim, u skladu sa rezultatima ovog istraživanja, zapažanje je da su nivoi bakterijskog antigen specifičnog IgA antitela niži kod pacijenata sa parodontopatijom nego kod pacijenata sa AKS[22,23].

Ovaj rezultat je, prema jednoj od retkih studija u kojoj su procenjivani uzorci subgingivnih plakova, imao direktnu vezu sa subkliničkom aterosklerozom[24]. Kod nelečene parodontopatije, Gram-negativne bakterije (*P.g, A.a.*) nalaze se u parodontalnim džepovima, ali se mogu naći i u ateromima[25]. U vezi sa aterosklerozom, najčešće proučavani parodontopatogeni su *A.a.* i *P.g.*, koji su serološki heterogene vrste. DNK ovih vrsta pronađen je u ljudskim aterosklerotičnim plakovima.

Bakterije ili njihovi delovi mogu imati pristup cirkulaciji krvi kroz inflamirano parodontalno tkivo tokom svakodnevne rutine.

Jednom kada su u cirkulaciji, bakterijske komponente mogu izazvati i podsticati sistemsku inflamaciju i proaterogeni odgovor[26,27].

periodontal disease.This could reflect on the differences in study design and measures of coronary heart disease and periodontitis.

A significant relationship between poor periodontal status and ACS was demonstrated by using periodontal indices and periodontal pathogens. The existing studies provide evidence of which the periodontal parameters would describe best an association between inflammation of the periodontal tissues and ischemic stroke event. Even more, none of the larger studies have studied the periodontal situation at the time of the ischemic event.

All periodontal parameters were significantly higher in the patients with ACS. According to our findings, elevated periodontal parameters can be considered as the independent risk factors for developing cardiovascular disease. This is in agreement with a previous study, which has reported higher levels of inflammatory markers in patients with more severe periodontitis. Inflammation is recognized as a significant, active participant as well as a risk factor in many chronic diseases, including atherosclerotic cardiovascular disease and periodontitis[19,20,21].

In this study, it was demonstrated that periodontopathogens (*A.a, P.a.*) were present in high percentage in cases with ACS, much more than in cases only with periodontitis. The results demonstrated that these periodontopathogens might be the risk factors for future ACS event because greater percentage of periodontopathogens was accompanied by an inflammatory reaction of periodontal tissues. However, consistent with our data is the observation that levels of bacterial antigen-specific IgA antibody are lower in patients with periodontitis than in patients with ACS [22,23].

This result is in accordance with one of the few studies where subgingival plaque samples have been assessed, periodontal microbiology had a direct relationship with subclinical atherosclerosis[24]. In untreated periodontitis, Gram-negative bacteria (*P.a., A.a.*) are found in periodontal pockets, but they may also be found in atheroma[25]. Concerning atherosclerosis, the most widely studied periodontopathogens are A.a. and P.g., which are serologically heterogeneous species.

DNA of these species has been found in human atherosclerotic plaque. Bacteria or their parts may have an access to circulation via inflamed periodontal tissue during daily routines.

Umerena i jaka parodontopatija povećavaju nivo sistemske inflamacije. Sve hronične zapaljenske bolesti, pa i parodontopatija, povezane su sa povećanom sistemskom inflamacijom merenom biomarkerima.

Ispitivana je povezanost dubine parodontalnih džepova i AKS, jer su duboki parodontalni džepovi posebno održivi portali za ulazak bakterija u sistemsku cirkulaciju krvi. Parodontalni indeksi bili su značajni kod ispitanika sa AKS, nakon korekcije za moguće kofaktore. Parodontopatija se može pridodati sistemskom inflamatornom opterećenju pojedinaca.

Rezultate ove studije treba uzeti u obzir pri planiranju strategija za sprečavanje srčanih bolesti. Stomatološke konsultacije i eliminacija parodontalne infekcije trebalo bi da budu deo sveobuhvatnog lečenja svih pacijenata sa srčanim problemima[1].

Čak i bez podataka iz takvih studija, preporučuje se da se parodontalna infekcija navede kao mogući faktor akutne miokardijalne infekcije, zajedno sa pušenjem, prekomernom težinom, visokom koncentracijom lipida i visokim krvnim pritiskom. Parodontalna infekcija može se javiti i bez većih znakova ili simptoma, čak i ako je zahvaćena velika površina.

Za ulogu parodontopatije u kardiovaskularnim bolestima predloženo je nekoliko hipoteza, zasnovanih na inflamatornim modelima bolesti. Jedna hipoteza govori o tome da neki pojedinci mogu imati fenotip monocita, koji izlučuje viši od normalnog nivoa proinflamatornih medijatora u odgovoru na bakterijske infekcije[28]. Parodontopatija je infektivno oboljenje, a kao odgovor na parodontopatogene i njihove endotoksine, oslobađanje proinflamatornih medijatora dovodi do propadanja parodontalnog vezivnog tkiva i kostiju. Za indukciju sistemske inflamacije predloženo je da bude patogeni mehanizam kojim se može objasniti veza infekcije parodontalnog tkiva i ateroskleroze, gde bakterije i proinflamatorni citokini igraju važnu ulogu[29,30].

Druga hipoteza je da parodontopatogeni mogu sistemski da se šire u krvotok i direktno inficiraju vaskularni endotel, što dovodi do ateroskleroze i ishemije i infarkta miokarda.

U parodontopatiji, porast Gram-negativnih bakterija može izazvati sistemsku inflamaciju koja vodi ka kardiovaskularnim bolestima[31,32].

Lečenje parodontopatije smanjuje sistemske inflamatorne markere, ali ako se ne

Once in the circulation, bacterial components can induce and promote systemic inflammation and proatherogenic responses[26,27]. Moderate to severe periodontitis increases the level of systemic inflammation. All chronic inflammatory diseases, and periodontitis, have been associated with increased systemic inflammation as measured by biomarkers.

Association was observed between periodontal pocket depths and ACS because deep periodontal pockets are especially viable portals for entry of bacteria into the systemic blood circulation. Periodontal parameters were significant in subjects with ACS after correction for possible confounders. Periodontitis may add to the systemic inflammatory burden of affected individuals.

The results of this study should be taken into consideration when planning strategies to prevent cardiac disease. Dental consultations and elimination of periodontal infection should be part of the comprehensive treatment of all patients with cardiac problems[1].

Even without data from such studies, it is recommended that periodontal infection can be listed as a possible contributing factor to acute myocardial infection, along with smoking, overweight, high lipid concentration and high blood pressure. Periodontal infection may occur without major signs or symptoms, even if a large area is affected.

Several hypotheses, based on inflammatory models of disease, have been proposed for the role of periodontitis in cardiovascular disease. One hypothesis is that some individuals may have a monocyte phenotype that secretes higher than normal levels of pro-inflammatory mediators in response to bacterial infections 28. Periodontitis is an infectious disease, and in response to periodontopathogens and their endotoxins, the release of pro-inflammatory mediators leads to periodontal connective tissue and bone degradation. Induction of systemic inflammation has been proposed to be the pathogenic mechanism behind the association of periodontal tissue infection and atherosclerosis, where bacteria and pro-inflammatory cytokines play an important role[29,30].

Another hypothesis is that the periodontopathogens may disseminate systemically through the bloodstream and infect the vascular endothelium directly, leading to atherosclerosis and myocardial ischemia and infarction. In periodontitis,

leči ili neadekvatno kontroliše, umerena i teška forma parodontalnog oboljenja progredira i povećava sistemsku inflamatornu reakciju i tada parodontopatija može biti nezavisno povećan rizik za nastanak AKS. Pacijente sa AKS treba obavestiti da može postojati povećan rizik za AKS ako imaju parodontopatiju. Pacijente sa AKS i parodontopatijom treba podvrgnuti lečenju parodontopatije kako bi se smanjio rizik od pojave AKS.

Zaključak

Zaključno, rezultati ovog istraživanja sugerišu da je parodontalno oboljenje u kombinaciji sa parodontopatogenima povezano sa povećanim rizikom za akutne kardiovaskuarne događaje. Konkretno, visoki parodontalni indeksi u kombinaciji sa nivoima inflamacije parodontalnog tkiva ukazuju na visok rizik od incidenta ishemičnih događaja.

Ova studija potvrđuje nalaze drugih istraživanja, koja sugerišu povezanost lošeg oralnog statusa i AKS i pružaju dokaze da bi inflamatorni i hemostatski faktori mogli da igraju važnu ulogu u ovom udruživanju.

overgrowth of Gram-negative bacteria may cause systemic inflammation leading to cardiovascular diseases[31,32].

Treatment of periodontitis reduces the systemic inflammatory markers, but if left untreated or inadequately controlled, moderate to severe periodontitis increases the systemic inflammatory burden and that periodontitis may be an independent increased risk for ACS. Patients with ACS should be informed that there may be an increased risk for ACS if they have periodontitis. Patients with ACS and periodontitis should be subjected to the treatment of periodontitis in order to reduce the risk for ACS.

Conclusion

In conclusion, our results suggest that periodontitis in combination with periodontopathogens are associated with increased risk for acute ACS events. In particular, high periodontal parameters combined with levels of periodontal tissue inflammation indicate a high risk of incident ACS events.

The present study confirms the finding of recent reports that suggest an association between poor oral status and ACS, and provide evidence that inflammatory and hemostatic factors could play an important role in this association.

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