Unlike Periodontitis, Caries Does Not Associate With Intracranial Aneurysms or Aneurysmal Subarachnoid Hemorrhage

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Abstract

Background:

Periodontal infections have been associated to the formation and rupture of intracranial aneurysms (IA). In this study we investigated whether also caries (tooth decay) associates to IA pathology.

Methods:

A total of 166 patients with either IA or aneurysmal subarachnoid hemorrhage (aSAH) underwent oral examination in Kuopio University Hospital and Tampere University Hospital. Findings were compared to age, gender and geographically matched controls acquired from cross-sectional Health 2000 Survey. This study consisted three sequential steps. First step was a comparison of the caries prevalence and number of missing teeth in IA and aSAH patients with the control population, second step was a multivariate analysis with demographic factors and third step was a prospective 13-year follow-up of participants with any caries or missing teeth.

Results:

In logistic regression adjusted for known risk factors and demographic data, caries (OR: 0.412 95%CI 0.2-0.9, p=0.028) was associated with lack of IAs, while age (OR:1.029 95%CI 1.0-1.1 p=0.039), current smoking (OR:2.7 95%CI 1.4-5.1, p=0.003) and severe periodontitis (OR:4.3 95%CI 2.3-12.5, p<0.001) associated with IA formation. Severe periodontitis associated also to aSAH in logistic regression (OR: 5.4, 95%CI 1.9-15.5, p=0.002). In the cox-regression, severe periodontitis at baseline increased the risk of aSAH (HR: 11.9, 95%CI 1.2-114.7, p=0.032) during a 13-year follow-up.

Conclusion:

Unlike periodontitis, caries does not increase the risk of IAs and aSAHs. However, cariogenic bacteria may participate to IA pathology by disseminating to circulation via inflamed gingival tissue.

Introduction

Unruptured intracranial aneurysms (UIA) are frequent: They are found in approx. 3% of the past middle age population as mostly asymptomatic cerebral artery lesions.[24]. Despite the rather high prevalence of UIAs, intracranial hemorrhage resulting from IA rupture is a relatively rare event (incidence approx. 10/100 000 in most countries) [18]. This form of intracranial hemorrhage known as aneurysmal subarachnoid hemorrhage (aSAH) has, however, a particularly sinister prognosis with a mortality reaching almost 50% and with many of the survivors left significantly disabled [23]. The best treatment for aSAH is to prevent it, a goal for which it is paramount to predict which UIA is going to eventually rupture and who will develop UIAs in the first place.

Chronic inflammation or inflammatory cell mediated remodeling of the cerebral artery has been shown to be a crucial mediator of IA formation, as well as of the IA wall degeneration that eventually leads to rupture [3,6,7,12]. The presence of bacterial derived DNA in the IA walls, as well as the expression of Toll-like receptors that react to bacterial components and activate the immune system has been shown earlier [21]. This strongly implies that dental pathogens play a role in the inflammation mediated artery and aneurysm wall remodeling that leads to IA formation and aSAH. In addition, a prior study using RT-qPCR demonstrated that this bacterial DNA originates from several dental pathogens [21].

Steptococcus mutans is a classical dental pathogen involved in caries, a highly prevalent dental infection that leads to formation of cavities in teeth, and if untreated, to inflammation and necrosis of the tooths nerve system, pulp. Eventually these conditions may lead to root canal treatment or extraction of the affected tooth. Certain *S. mutans* strains like the Cnm and Cbm proteins possess proteins capable of binding collagen and are linked to aggressive form of caries [15]. *S. mutans* expressing collagen-binding protein (CBP) has been previously shown to be more prevalent in oral samples of cerebral haemorrhage patients [17] and the persons affected by aSAH or other forms of intracranial hemorrhage [11]. CBP of *S. mutans* has been shown in animal models to predispose to intracranial hemorrhage through affecting the cerebral artery wall directly and can be detected in cerebral haemorrhage tissue after oral administration [17]. It seems possible that this pathogen, so important in caries, would also play role in IA formation and rupture.

Since it was recently observed that gingivitis and periodontitis*, i.e.* chronic infection of the gums and tooth supporting tissues, associates with the risk of developing IAs and eventually aSAH [9,22] and prior literature suggest involvement of also the caries pathogen *S. mutans* in IA formation and rupture, we now investigated whether caries is associated with the IA formation and the eventual risk of aSAH from IA rupture.

Materials And Methods

This study was performed in three sequential steps. First step was a comparison of the caries prevalence and number of missing teeth between IA and aSAH patients and the control group. Second step was a multivariate analysis between demographic factors, caries, missing teeth and periodontitis and IA and aSAH prevalence and third step was a prospective 13-year follow-up of patients with caries prevalence or number of missing teeth. This study was approved by the ethical review boards of the Healthcare District of Northern Savo, Pirkanmaa hospital district and The Ethical Committee for Research in Epidemiology and Public Health at the Hospital District of Helsinki and Uusimaa in Finland (Health 2000 and 2011 Surveys). Written informed consent was obtained from all participants.

Study population for the case series of IA patients

Patients referred to the Departments of Neurosurgery of Kuopio university hospital (KUH) and of Tampere university hospital (TaUH) for IA treatment during the period between June 2010 and October 1st 2016 were recruited to this study. A clinical oral examination was performed on 76 IA patients in KUH (42 with

unruptured IAs and 34 with aSAH) and for 90 IA patients in TaUH (60 with unruptured IAs and 30 with aSAH). Patient selection was random due to the limited availability of an examining dentists (JH and MP) and interexaminer validation was not done. In KUH IA patients caries lesions were common but caries diagnostics could not be done due to the lack of panoramic x-rays and KUH IA patients were therefore not included in the analysis. In TaUH IA patients, number of teeth and caries was examined from panoramic x-ray. Caries was diagnosed when the caries lesion was clearly extending to dentin (a bone-like matrix under tooth enamel). Periodontitis was diagnosed taking into account the deepest periodontal probing depth, categorized as follows: < 4 mm no periodontitis, 4-5 mm periodontitis, and = 6 mm severe periodontitis [9,22]. For the KUH and TaUH IA patients, clinical data including known risk factors (age, gender and current smoking) was collected from the medical reports and a personal interview.

Case-control comparison of IA patients

A previously published prospectively collected cohort of 8028 adult Finns of whom a total of 5144 participants underwent a baseline oral examination. From this group of 5144 participants, we selected the geographically matched controls from TaUH area (n=340) as our control group for the studied IA and aSAH patients of Tampere University Hospital. Demographics and risk factors for IA were collected using a questionnaire as described previously [2]. To identify possible prior uIA or aSAH before baseline the national registry for hospital discharge diagnosis (HILMO) was searched for ICD-10 codes I67.1 or I60.0-I60.9. Also procedure codes were searched for surgical or endovascular procedures according to the Nordic Classification for Surgical Procedures.

Prospective follow-up of Health 2000 –survey participants

Follow-up data was collected from HILMO registry after the baseline examination but before December 31st 2013 as previously described [9]. Cox-regression was used to calculate the hazard ratio for IA formation and for aSAH during the 13-year follow-up after the baseline examination.

Statistical analyses

Data was presented as frequencies or medians with ranges. Fisher's exact test or chi-square tests were used to compare categorical variables and Mann-Whitney *U test* for continuous variables. Multivariate logistic regression and Cox-regression were performed as described above. Results from both regression analyses were presented as odds- or hazard ratios with 95% confidence intervals. SPSS 22.0 statistical software (IBM) was used and a p value < 0.05 was considered as significant.

Results

Missing teeth and prevalence of caries among UIA and aSAH patients

UIA patients from both KUH and TaUH cohorts had a median of 2 missing teeth and aSAH patients had median of 1 missing teeth. After dividing the study group to quartiles according to the number of missing teeth, there was a trend towards higher number of missing teeth among UIA and aSAH patients, but this remained non-significant. (data not shown).

In the subgroup of TaUH patients, at least one dentin caries lesion was found in 18.3% of the UIA patients (Table 1) and 30.0% of the aSAH patients (Table 2). 25.6% of the controls from the same region had at least one dentin caries lesion (Tables 1 & 2). but the difference was insignificant

Periodontitis but not caries associates with the risk of IA formation and aSAH in multivariate analysis

Logistic regression model was adjusted for age, gender and current smoking with geographically matched controls. Dentin caries had negative correlation to IA formation (OR: 0.4 95%CI 0.2-0.9, p=0.028, Table 3, model 1). Current smoking associated with UIAs (OR: 2.7, 95%CI 1.4-5.1, p=0.003, Table 3, model 1), but not with aSAH. Severe periodontitis remains as a predictor to UIA and aSAHs (OR: 4.3, 95%CI 2.3-12.5, p<0.001 and OR: 5.4, 95%CI 1.9-15.5, p=0.002, respectively, Table 3, models 1&2) also in the TaUH cohort. On the contrary, number of missing teeth was not associated with uIAs nor aSAH (Table 3 Model 1&2).

Unlike severe periodontitis, caries did not associate with later aSAH in a 13-year follow-up.

In a Cox-regression model adjusted for age, gender, current smoking, caries, peridodontitis and missing teeth at baseline, only severe periodontitis at baseline increased the risk of aSAH (Table 4). Patients were identified by having both ICD10 and procedure code relevant to aSAH.

Discussion

In this study caries associates inversely with the formation of IAs, but not with aSAH. Caries is the most common disease globally affecting nearly 3.5 billion people worldwide [13]. Despite the fact that caries is more prevalent in high-socioeconomic states [13], our study of high-socioeconomic population, did not associate caries to a greater risk of IA and aSAH. There are several explanations for the lack of association: first the nature of caries is a local infectious disease of the tooth structure with systemic responses only when the caries reaches the tooth pulp. Secondly, caries is most often treated with fillings before severe conditions, such as inflammation of tooth pulp or periapical abscesses occur. However these caries-related conditions remain a challenge to oral health care providers. Thirdly, caries does not predispose to bacteremia contrary to periodontal diseases of the gingival tissues.

The association studies of oral bacteria with vascular diseases, including sIA/aSAH concentrate mostly on periodontal bacteria. Regarding cariogenic bacteria, a Japanese study [11] linked specific cnm strain of *Streptococcus mutans* to sIA. This specific strain promotes platelet aggregation inhibition and matrix metalloproteinase-9 activation which can logically be linked with sIA formation and rupturing. Although in our study caries did not associate with sIA disease, the finding of Inenaga et al may be explained by the

poor oral hygiene predisposing to a poorer periodontal status. Via inflamed periodontal tissues this specific *S. mutans* strain could disseminate to circulation and to IA walls. This explanation is, however, highly speculative.

Other dental infections as risk factors for IA formation and subsequent aSAH

Whereas caries does not appear to associate with IA and aSAH, gingivitis and periodontitis, however, have been shown to associate to both IAs and aSAH [8-10,22]. Similar association of periodontitis to IAs and aSAHs that we have previously reported in the KUH cohort [9], was also clear in this study with TaUH patient cohort with geographically matched healthy controls. Furthermore, previously a plethora of studies have associated periodontitis to cardiovascular diseases [14,20] and this further demonstrates the crucial role of gingival pocket health as the border between systemic circulation and oral cavity. The association between oral infections and vascular diseases could be explained by either (i) direct effect on local bacterial infection on systemic low grade inflammation response, (ii) bacteremia and subsequent distant local infections (such as endocarditis) or (iii) similar genetic background of the diseases. Periodontal pathogens correlate to diseases/medical states of which pathogenesis is strongly linked to collagen degradation caused by MMP activation in different sites of the human body [4,11,25], such as pre-term birth and low birthweight [5], cardiovascular diseases [16] and periodontitis [19]. A single specific finding that further explains the association was introduced by Aarabi and colleaques in 2017. They described common genetic background of periodontal destructive and vascular destructive states [1]. The involvement of shared genetic background of the diseases could also explain the associations: Some people are prone to both periodontal disease and cardiovascular diseases, and the bacteria invade the vascular wall if they are given the chance by genetic factors. Pathomechanisms of caries are not similar with these collagen degradative states seen in periodontal diseases.

Since periodontal diseases associate with sIA disease and increase the risk of aSAH in the long term, but other oral diseases, to our knowledge, do not, the effect and association might be explained by the nature of the disease itself rather than periodontal disease being only an “innocent co-variant” reflecting for example poor socioeconomic status to which many IA risk factors associate to. A prior study on the bacterial DNA present in IA wall tissue have not been able to discriminate whether periodontal or cariogenic pathogens associate with IAs, but rather DNA of pathogens related to both groups are found in the IA wall [21]. This discrepancy between the bacterial DNA findings and the clinical finding that nevertheless only periodontal disease associates with IA formation or rupture could be explained by the bleeding wound surface in inflamed gingival pocket forming a gateway for oral bacteria to enter the systemic circulation, and eventually the IA wall. Further studies on this hypothesis are warranted.

Limitations of the study

Our study has some limitations due to its design. First, we could not recruit all IA and aSAH patients to the study due to patients denial to participate or due to tight schedule of the examining dentists. The use of healthcare registry data has always a source of bias. Also, our comparison between KUH and TaUH patients to participants of Health 2000 –survey has its limits, since there is a 15-16 year gap between oral

examinations. Also, single person performing the oral examination (JH in KUH and MP in TaUH) could lead to over- or underestimations of oral conditions.

Conclusion

Unlike periodontitis, caries does not associate with the IA formation or aSAH. However, cariogenic bacteria may participate to IA pathogenesis, but further research is needed

Declarations

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Conflicts of interest: Authors declare no conflict of interest to this study.

Availability of data and material: Due to the nature of this research and GDPR policy, participants of this study did not agree for their data to be shared publicly, so supporting data is not available.

Code availability: Not applicable

Ethics approval: This study was approved by the ethical review boards of the Healthcare District of Northern Savo, Pirkanmaa hospital district and The Ethical Committee for Research in Epidemiology and Public Health at the Hospital District of Helsinki and Uusimaa in Finland (Health 2000 and 2011 Surveys).

Consent to participate: Written informed consent was obtained from all participants.

Consent for publication: Written informed consent was obtained from all participants.

Authors' contributions: JF and JH concepted the study design, MP and TP gathered the data of TAUH cohort. JH gathered data of KUH and performed data harmonization, statistical analysis and drafted the manuscript. JH, TP, MV, ALS, JF and MP contributed equally to manuscript revision.

References

1. Aarabi G, Zeller T, Seedorf H, Reissmann DR, Heydecke G, Schaefer AS, Seedorf U (2017) Genetic Susceptibility Contributing to Periodontal and Cardiovascular Disease. J Dent Res 96:610–617. Doi:10.1177/0022034517699786 [doi]
2. Aromaa AKS (2002) Health2000 -study. http://urn.fi/URN:ISBN:951-740-262-7. Accessed Accessed 23.1.,. 2019
3. Chalouhi N, Ali MS, Jabbour PM, Tjoumakaris SI, Gonzalez LF, Rosenwasser RH, Koch WJ, Dumont AS (2012) Biology of intracranial aneurysms: role of inflammation. J Cereb Blood Flow Metab 32:1659–1676. Doi:10.1038/jcbfm.2012.84 [doi]

4. Chen J, Khalil RA (2017) Matrix Metalloproteinases in Normal Pregnancy and Preeclampsia. Prog Mol Biol Transl Sci 148:87–165. Doi:S1877-1173(17)30050-9 [pii]
5. Daalderop LA, Wieland BV, Tomsin K, Reyes L, Kramer BW, Vanterpool SF, Been JV (2018) Periodontal Disease and Pregnancy Outcomes: Overview of Systematic Reviews. JDR Clin Trans Res 3:10–27. Doi:10.1177/2380084417731097 [doi]
6. Frösen J, Cebral J, Robertson AM, Aoki T. Flow induced inflammation mediated artery wall remodeling in the formation and progression of intracranial aneurysms.. Neurosurgical Focus
7. Frosen J, Piippo A, Paetau A, Kangasniemi M, Niemela M, Hernesniemi J, Jaaskelainen J (2004) Remodeling of saccular cerebral artery aneurysm wall is associated with rupture: histological analysis of 24 unruptured and 42 ruptured cases. Stroke 35:2287–2293. Doi:10.1161/01.STR.0000140636.30204.da [doi]
8. Hallikainen J, Keranen S, Savolainen J, Narhi M, Suominen AL, Ylostalo P, Kellokoski J, Pyysalo M, Pussinen P, Rauramaa T, Frosen J (2020) Role of oral pathogens in the pathogenesis of intracranial aneurysm: review of existing evidence and potential mechanisms. Neurosurg Rev. Doi:10.1007/s10143-020-01253-y [doi]
9. Hallikainen J, Lindgren A, Savolainen J, Selander T, Jula A, Narhi M, Koivisto T, Kellokoski J, Ylostalo P, Suominen AL, Frosen J (2019) Periodontitis and gingival bleeding associate with intracranial aneurysms and risk of aneurysmal subarachnoid hemorrhage. Neurosurg Rev. Doi:10.1007/s10143-019-01097-1 [doi]
10. Hallikainen J, Pyysalo M, Keränen S, Kellokoski J, Koivisto T, Suominen AL, Pussinen P, Pessi T, Frösen J (2021) Systemic immune response against the oral pathogens Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans is associated with the formation and rupture of intracranial aneurysms. Eur J Neurol. Doi:10.1111/ene.14986 [doi]
11. Inenaga C, Hokamura K, Nakano K, Nomura R, Naka S, Ohashi T, Ooshima T, Kuriyama N, Hamasaki T, Wada K, Umemura K, Tanaka T (2018) A Potential New Risk Factor for Stroke: Streptococcus Mutans With Collagen-Binding Protein. World Neurosurg 113:e77–e81. Doi:S1878-8750(18)30201-8 [pii]
12. Kanematsu Y, Kanematsu M, Kurihara C, Tada Y, Tsou TL, van Rooijen N, Lawton MT, Young WL, Liang EI, Nuki Y, Hashimoto T (2011) Critical roles of macrophages in the formation of intracranial aneurysm. Stroke 42:173–178. Doi:10.1161/STROKEAHA.110.590976 [doi]
13. Kassebaum NJ, Smith AGC, Bernabé E, Fleming TD, Reynolds AE, Vos T, Murray CJL, Marcenes W, GBD 2015 Oral Health Collaborators (2017) Global, Regional, and National Prevalence, Incidence, and Disability-Adjusted Life Years for Oral Conditions for 195 Countries, 1990-2015: A Systematic Analysis for the Global Burden of Diseases, Injuries, and Risk Factors. J Dent Res 96:380–387. Doi:10.1177/0022034517693566 [doi]
14. Kebschull M, Demmer RT, Papapanou PN (2010) "Gum bug, leave my heart alone!"–epidemiologic and mechanistic evidence linking periodontal infections and atherosclerosis. J Dent Res 89:879–902. Doi:10.1177/0022034510375281 [doi]

15. Lamba GS, Dufour D, Nainar SMH, Cioffi I, Lévesque CM, Gong SG (2020) Association of Streptococcus mutans collagen binding genes with severe childhood caries. Clin Oral Investig 24:3467–3475. Doi:10.1007/s00784-020-03217-4 [doi]
16. Lockhart PB, Bolger AF, Papapanou PN, Osinbowale O, Trevisan M, Levison ME, Taubert KA, Newburger JW, Gornik HL, Gewitz MH, Wilson WR, Smith SC Jr, Baddour LM, American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, Council on Epidemiology and Prevention, Council on Peripheral Vascular Disease, and Council on Clinical Cardiology (2012) Periodontal disease and atherosclerotic vascular disease: does the evidence support an independent association?: a scientific statement from the American Heart Association. Circulation 125: 2520-2544. Doi:10.1161/CIR.0b013e31825719f3 [doi]
17. Nakano K, Hokamura K, Taniguchi N, Wada K, Kudo C, Nomura R, Kojima A, Naka S, Muranaka Y, Thura M, Nakajima A, Masuda K, Nakagawa I, Speziale P, Shimada N, Amano A, Kamisaki Y, Tanaka T, Umemura K, Ooshima T (2011) The collagen-binding protein of Streptococcus mutans is involved in haemorrhagic stroke. Nat Commun 2:485. Doi:10.1038/ncomms1491 [doi]
18. Nieuwkamp DJ, Setz LE, Algra A, Linn FH, de Rooij NK, Rinkel GJ (2009) Changes in case fatality of aneurysmal subarachnoid haemorrhage over time, according to age, sex, and region: a meta-analysis. Lancet Neurol 8:635–642. Doi:10.1016/S1474-4422(09)70126-7 [doi]
19. Oliveira RR, Fermiano D, Feres M, Figueiredo LC, Teles FR, Soares GM, Faveri M (2016) Levels of Candidate Periodontal Pathogens in Subgingival Biofilm. J Dent Res 95:711–718. Doi:10.1177/0022034516634619 [doi]
20. Pussinen PJ, Alfthan G, Jousilahti P, Paju S, Tuomilehto J (2007) Systemic exposure to Porphyromonas gingivalis predicts incident stroke. Atherosclerosis 193:222–228. Doi:S0021-9150(06)00387-X [pii]
21. Pyysalo MJ, Pyysalo LM, Pessi T, Karhunen PJ, Ohman JE (2013) The connection between ruptured cerebral aneurysms and odontogenic bacteria. J Neurol Neurosurg Psychiatry 84:1214–1218. Doi:10.1136/jnnp-2012-304635 [doi]
22. Pyysalo MJ, Pyysalo LM, Hiltunen J, Jarnstedt J, Helminen M, Karhunen PJ, Pessi T (2018) The dental infections in patients undergoing preoperative dental examination before surgical treatment of saccular intracranial aneurysm. BMC Res Notes 11:600–600z. Doi:10.1186/s13104-018-3704-z [doi]
23. Stegmayr B, Eriksson M, Asplund K (2004) Declining mortality from subarachnoid hemorrhage: changes in incidence and case fatality from 1985 through 2000. Stroke 35:2059–2063. Doi:10.1161/01.STR.0000138451.07853.b6 [doi]
24. Vlak MH, Algra A, Brandenburg R, Rinkel GJ (2011) Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis. Lancet Neurol 10:626–636. Doi:10.1016/S1474-4422(11)70109-0 [doi]

25. Yabluchanskiy A, Ma Y, Iyer RP, Hall ME, Lindsey ML (2013) Matrix metalloproteinase-9: Many shades of function in cardiovascular disease. Physiology (Bethesda) 28:391–403. Doi:10.1152/physiol.00029.2013 [doi]

Tables

Table 1 Demographics, dentin caries and number of missing teeth of TAUH unruptured IA (UIA) patients and geographically matched controls. Patients with SAH excluded from analysis.

Variable	UIA patients (n=60)	Matched controls (n=340)	P-value
Age	57.0 (23.0-74.0)	48.0 (30.0-89.0)	**0.019***
Gender (number of females)	43/60 (71.7%)	207/340 (60.9%)	0.065
Current smoking	29/60 (48.3%)	104/339 (30.7%)	**0.002***
At least one dentin caries	11/60 (18.3%)	87/340 (25.6%)	0.392
Median of missing teeth	2 (0 -28)	1 (0 – 27)	0.956
Missing teeth divided to quartiles			
0-7 missing teeth	49/60 (81.7%)	281/340 (82.6%)	0.963
8-14 missing teeth	5/60 (8.3%)	25/340 (7.4%)	0.963
15-21 missing teeth	4/60 (6.7%)	16/340 (4.7%)	0.963
22-28 missing teeth	2/60 (3.3%)	18/340 (5.3%)	0.963

Periodontitis	23/60 (38.3%)	133/340 (39.0%)	**<0.001***	
Severe Periodontitis	24/60 (40.0%)	51/340 (15.0%)		**<0.001***

Data presented as median and range or as proportions. P-values were calculated with Fisher's exact test and with Mann-Whitney U test for continuous variables respectively

Table 2 Demographics, dentin caries and number of missing teeth of TAUH aSAH patients and geographically matched controls. UIA patients excluded from analysis.

Variable	aSAH patients (n=30)	Controls (n=340)	P-value
Age	49.0 (31.0-66.0)	48.0 (30.0-89.0)	0.107
Gender (number of females)	14/30 (46.7%)	206/340 (60.6%)	0.133
Current smoking	16/30 (53.3%)	104/340 (30.6%)	**0.011***
At least one dentin caries	9/30 (30.0%)	87/340 (25.6%)	0.591
Median of missing teeth	1 (0 -26)	1 (0 – 27)	0.863
Missing teeth divided to quartiles			
0-7 missing teeth	24/30 (80.0%)	281/340 (82.7%)	0.871
8-14 missing teeth	3/30 (10.0%)	25/340 (7.4%)	0.871
15-21 missing teeth	2/30 (6.7%)	16/340 (4.7%)	0.871
22-28 missing teeth	1/30 (3.3%)	18/340 (5.3%)	0.871
Periodontitis	9/30 (30.0%)	133/340 (39.1%)	**<0.001***

Severe Periodontitis	14/30 (46.7%)	51/340 (15.0%)	**<0.001***

Data presented as median and range or as proportions. P-values were calculated with Fisher's exact test and with Mann-Whitney U test for continuous variables respectively

Table 3. Association of dentin caries and number of missing teeth to IA formation and aSAH with periodontitis in a multivariate analysis comparing TAUH IA patients with a geographically matched control group of Health 2000 participants.

Variable	Odds ratio	95% CI	P-value
-			
IA formation (Model 1) ***(60 unruptured IA cases in analysis)***			
Age	**1.029**	1.001 – 1.057	**0.039***
Gender (number of males)	**1.742**	0.894 – 3.395	0.103
Current smoking	**2.666**	1.395 – 5.095	**0.003***
One or more dentin caries	**0.412**	0.187 – 0.909	**0.028***
One or more missing teeth (wisdom teeth excluded)	**0.995**	0.944 – 1.049	0.866
Periodontitis	**2.127**	0.990 – 4.572	0.053
Severe periodontitis	**4.303**	2.348 – 12.541	**<0.001***
-			
aSAH (Model 2) ***(30 aSAH cases in analysis)***			
Age	**1.001**	0.964 – 1.039	0.957
Gender (number of males)	**0.707**	0.313 – 1.598	0.405
Current smoking	**2.054**	0.870 – 4.849	0.101
One or more dentin caries	**0.762**	0.311 – 1.866	0.552
One or more missing teeth	**0.998**	0.927 – 1.075	0.965

(wisdom teeth excluded)			
Periodontitis	**1.400**	0.483 – 4.062	0.536
Severe periodontitis	**5.390**	1.870 – 15.538	**0.002***

Table 4. Risk of aSAH during a 13-year follow-up. COX regression model of Health 2000 participants.

Variable	Hazard ratio	95% CI	P-value
-			
aSAH (8 events in analysis)			
Age	**1.026**	0.950 – 1.109	0.513
Gender (number of females)	**3.803**	0.742 – 19.477	0.109
Current smoking	**4.506**	0.967 – 20.982	0.055
One or more dentin caries	**0.407**	0.048 – 3.444	0.410
One or more missing teeth (wisdom teeth excluded)	**0.753**	0.512 – 1.106	0.148
Periodontitis	**1.631**	0.145 – 18.394	0.692
Severe periodontitis	**11.926**	1.204 – 114.676	**0.032***

Supplementary Files

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- 09102021FlowchartCaries.docx