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Review Article

Evolution of the Serotypes of *Aggregatibacter actinomycetemcomitans* In Relation to Aggressive Periodontitis and Geographic Origin of Individuals – A Review of the Literature

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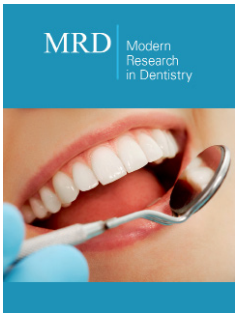

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Abstract

Background: Researchers have investigated the relationship among serotype distribution, ethnical status and geographic populations, and periodontal conditions. Studies that have examined the prevalence and the distribution of *A. actinomycetemcomitans (A.a.)* serotypes and the relation between the different serotypes of the bacterium and periodontal status were reviewed.

Material and methods: A systemic literature search for publications in the database PubMed between 1983 and January 2018 regarding the distribution of *A.a.* serotypes in subgingival samples of periodontitis patients and periodontally healthy subjects by various techniques (including culture, immunodiffusion, immunofluorence, polymerase chain reaction was carried out.

Results: From the cited studies, *A.a.* bacteria were isolated from various periodontal conditions, including aggressive periodontitis. Clinical isolates from diverse geographic populations with different periodontal conditions were summarized. Serotypes a, b and c were largely found, and serotype c was the most prevalent. The distribution of the most recently identified serotype g remains unknown.

Conclusion: The current literature reviews suggest that serotype a, b, and c are universally dominant, serotypes d, c and f are rare; the distribution of the most recently identified serotype g still needs more studies to provide its distribution and its effect on periodontitis. It is widely accepted that distribution patterns of *A.a.* vary among subjects of different ethnicity and geographic regions. The importance of the identification of *A.a*. and their antibiotic susceptibility tests prior to the treatments of periodontitis especially for aggressive periodontitis and peri-implantitis concomitantly to periodontal therapy are strongly advised.

Keywords: *Aggregatibacter actinomycetemcomitans (A.a.)*; Serotypes; Aggressive periodontitis (AgP); Periodontal diseases; Prevalence

Introduction

Aggressive periodontitis is a severe and rapidly progressing form of periodontitis [1,2] that affecting supporting tissues of the teeth induced by microbial deposits [3]. *Aggregatibacter actinimycetemcomitans* is an important pathogen related to aggressively progressive periodontal breakdown in adolescents and adults [4,5]. *A. actinomycetemcomitans (A.a.)* can be grouped into seven serotypes (a-g) [6,7]. Several studies have examined the relationship of *A.a.* serotype, ethnical status and geographic populations, periodontal disease status [8,9,10]. Individuals are usually colonized by a single serotype that can exist for life [8,11,12]. The frequency distribution of *A.a.* serotypes differs among various populations [13]. The available literature suggests that serotypes a, b. and c occur much more often among oral isolates than d, e, f and g [14,15,16]. The serotype distributions have been shown to be different among various geographic populations including African, Asian, Europeans, and North and South American [15,16,17,18,19]. The purpose of the present study was to review the studies that have investigated the prevalence and the distribution of *A.a.* serotypes in subgingival samples

of periodontitis (especially the aggressive periodontitis) patients and to examine the possible evolution of the serotypes.

Materials and methods

Data sources

The electronic database PubMed was searched systemically for studies published between 1983 and January 2018. The search terms included "serotypes" and "*Aggregatibacter actinomycetemcomitans*" or "*Acticbacillus actinomycetemcomitans*" and "periodontitis".

Study selection

Studies involving the distribution of *A.a.* serotypes in subgingival samples of periodontitis patients and periodontally healthy subjects by employing culture, indirect immunofluorescence and/or immunodiffusion assays, and polymerase chain reaction (PCR) were eligible for inclusion in this review. Data were extracted from each study:

(a) the first author and year of publication;

(b) the country where the study was investigated;

(c) searched serotypes and

(d) possible association between periodontal conditions and serotypes.

Result

Forty-two articles were identified. The full text/abstract of each of the 42 papers was reviewed. The study selections are presented in Table 1. The publication dates ranged from 1983 to 2018. Clinical isolates from diverse geographic populations with different periodontal conditions were evaluated. The samples were obtained of the subjects from Brazil, Germany, Greece, Indonesia, Japan, Korea, Taiwan, Thailand and United States (US) etc. Table 1 shows the prevalence and distribution of *A.a.* serotypes a, b and c were largely found, and serotype c was the most prevalent. These serotypes were isolated from various periodontal conditions, including aggressive periodontitis. Serotypes d, e, f and g were either not detected or were relatively infrequent. Some *A.a.* isolates were non-typed.

Table 1: Prevalence and distribution of A. actinomycetemcomitans (A.a.) serotypes and association with periodontal status. LAgP: Localized Aggressive Periodontitis. CP: Chronic Periodontitis, JP: Juvenile Periodontitis.

Study/Country	Occurrence of *A.a.* Serotypes	Periodontal Conditions and Serotypes
Zambon 1983 [8]/ US	A total of 301 isolates of *A.a.* from the oral cavity of 74 subjects	Each patient harbored only one serotype. Fourteen healthy subjects and 7 CP patients exhibited serotypes a and b in almost equal frequency, c was less frequently. In 29 LAgP patients, the number of patients with b serotype were 2 folds higher than that of serotypes a or c, suggesting a particular high periodontopathic potential of *A.a.* serotypes b strains.
Zambon et al. 1983 [11]/ US	*A.a.* was in 28 of 29 LAgP patients but only 15% of the other subjects (29 of 134 CP patients), 24 of 142 periodopntally healthy subjects. Individuals within a family all harbored the same serotype.	The high prevalence of *A.a.* in the sub- gingival plaque of LAgP patients, compared to the much lower prevalence in other patient groups supports the hypothesis that *A.a.* is an etiologic agent in AgP (JP).
Zambon 1985 [20]/ US	Serotype of *A.a.* has been categorized into 3 serotypes.	*A.a.* as an important microorganism in the etiology of LAgP (LJP).
Tsai et al. 1987 [21]/ Taiwan	Immunodiffusion data indicated that greater than 60% of AgP, advanced destructive patients reacted to antigens found in the *A.a.* (mainly to serotype c or strain 652).	The periodontal destruction in Chinese periodontitis patients especially JP and ADP are associated with infection by and immune response to *A.a.*
Chung et al. 1989 [22]/ Korea	*A.a.* occurred in 75% of LJP lesions and 6% of normal sites with approximately equal distribution of serotype a, b, and c. Single serotypes were isolated from 9 patients while 3 patients harbored 2 serotypes either in the same or different disease sites. *A.a.* leukotoxicity occurred in 22% isolates with a 62% prevalence. Individual sites harbored both leukotoxic and non-leukotoxic strains of *A.a.* with no serotype association.	The distribution of serotypes and leuko- toxic strains of *A.a.* in Korean LJP patients differed from those reported in the US. This suggests that serotype b may not be more important in the pathogenesis of LJP.
Asikalinen et al. 1991 [23]/Finland	All 3 seropes (a, b, c) were commonly found. Serotype b was dominant in subjects with periodontal disease and serotype c was the most common serotype in the healthy subjects.	This study suggests differences in the distri- bution of *A.a.* serotypes between periodontal health and disease.

Saarela et al. 1992 [24]/Finland	86 subjects (95%): one serotype only, 466 (91%) isolates from 80 subjects were serotype a (25% of isolates/30 subjects), b (25% of isolates/27 subjects), c (41% of isolates/30 subjects), d (15 isolates/4 subjects), e (18 isolates/5 subject), untypable (16 isolates/5 subjects). 1 to 6 years followed: same infected serotypes, stability of infected serotypes was demonstrated.	1 to 6 years followed up: same infected serotypes stability of infected *A.a.* was demonstrated.
Yamamoto et al. 1997 [25]/Japan	A total of 157 *A.a.* isolates from 39 patients with periodontitis: Serotypes: 42 (a), 6 (b), 39 (c), 9 (d), 41 (e), 20 (untypable).	37 patients are with single serotype, 2 patients with 2 different serotype strains (b/e, b/untypable) which were identical to that *A.a.* Y4 (serotype). Conclusion: The presence of multiple *A.a.* serotypes.
Mombelli et al. 1998 [26]/China	*A.a.*-(+):37/60 subjects. 21 subjects: (+) for both *A.a.* and *P.g.*. Serotypes: a (9, 24.32%), c (23, 62.16%), e (5, 13.51%), b, d, (0, 0%).	The results show a high frequency of the putative periodontal pathogens *P.g.* and *A.a.* and corroborate the concept that there is variation in virulence and pathogenic potential among isolates from different subjects.
Mombelli et al. 1999 [27]/China	117/185(63.24%) subjects were *A.a.*-(+) All 115 isolates were leukotoxin gene IktA. Serotyes: a (21, 17.0%), b (9, 7.6%), c (67, 57.3%), e (11,9.40%), d (0, 0%), non-typed (9, 9.4%).	A high prevalence irrespective of gender, and cohort suggests that *A.a.* is a common constituent of the normal flora and suggests differences in the microbial composition of subgingial plaque may exist for this population group as compared to north American and European populations.
Saarela et al. 1999 [28]/Finland	922 *A.a.* isolates from 115 subjects. Followed-up for 0.5 to 11.5 yrs. 99 subjects were treated. 104 subjects with only one serotype, or non-typeable isolates: a (25%), b (33%), c (23%), d (5%), 2 (7%), non-typeable (8%). 2 serotypes in 9 subjects were detected at sampling occasion. 1 subject: initial serotype was not recovered, a different serotype was once seen alone. 1 subject: initial serotype was not recovered later.	Identical genotypes of *A.a.* were repeatedly detected in each 52 subjects followed up isolates were the same serotypes.
Kaplan et al. 2001 [29]/US	A PCR assay using serotype-specific PCR primers showed that3 out of 20 LJP patients surveyed (15%) harbored A.a. strains carrying the serotype f gene cluster.	New serotype f was reported.
Dahlen et al. 2002 [30]/Thailand	*A.a.*-(+): 53/60 (88%) subjects, 11 subjects harbored 2 or 3 different strains. Serotypes a and c were the most prevalent, and serotype b was found only once among 46 tested isolates.	Tis study demonstrated a high prevalence of *A.a.* among adults of the rural population of south Thailand and indicates that. *A.a.* present as part of the resident flora in this population.
Yoshida et al. 2003 [31]/Japan	Among 328 subjects: *A.a.*-(+) in 19.5%, *P.g.*-(+): 27.1%. 39/75 *A.a.* positive sites (52%) with only one serotype. Sites with 2 and 3 different serotypes were 18 and 7 (9.3%) respectively. *A.a.* serotype[i] c was detected more often (76.9%) in sites that were positive for both *P.g.* and *A.a.* than in sites that were only A.a.-positive (33%).	The distribution of *A.a.* serotypes serotype was influenced by the presence of *P.g.*. The results suggest that the characteristic of serotype c may differ from those the other serotypes.
Yang et al. 2004 [32]/US	115 (33 AgP, 82 CP)/345 subjects were *A.a.*-(+). 86.96% of subjects with a single serotype (22 a, 44 b, 30 c, 1 d, 3 e), 11 (9.57%) with 2 serotypes, 2 (1.74%) with 3 serotypes, 2 with no detectable antigen.	The proportions of serotype b of *A.a.* are significantly greater in culture-(+) patients with AgP than those with CP (b serotype was predominant in age under 18 yrs. and between 19-35yrs old, but were not in age older than 35 years. 62 adult patients: one with d, 3 with e. Serotype b as the most common in AgP (60.61%). The proportion of subjects with serotype b was significantly higher in AgP compared to CP. Other serotypes were not significantly associated with new diagnostic categories. Serotypes d and e were not detected in AgP patients.
Yang et al. 2005 [15]/Taiwan	171 subjects (70 AgP, 101 CP, 50 HC). *A.a.*-(+): 84.3% in AgP, 60.4% in CP, 64.0% in HC.	The results suggest that prevalence and pro portions of *A.a.* are significantly greater in AgP patients than in those with CP. Serotype b is the predominant serotype of *A.a.* in patient with diseased periodontal conditions. Serotype c is a more common serotype detected in periodontal healthy subjects (HC).

Teixeira et al. 2006 [33]/Brazil	146 isolates from 23 patients (AgP or CP) and 26 specimens from subjects with or without periodontitis serotypes b and c were observed in similar frequencies, no subject harbored d, e or f serotype. 78% with single serotype, 1 AgP with mixed serotypes.	An association between serotype b and healthy periodontium and between serotype c and CP was observed.
Fine et al. 2007 [34]/US	1.2% LJP schoolchildren: 13.7% carried *A.a.* (16.7% of African and 22% of Hispanic students) A.a. serotypes a, b, and c were equally distributed among African-Americans; Hispanic students harbored predominantly serotype c.	Detection of *A.a.* in periodontally healthy children can serve as a risk marker for initiation of LAP. (Students without *A.a.* at baseline had a significantly greater chance to remain healthy compared to the *A.a.*-positive test-group and none of 58 *A.a.*-negative students showed bone loss. survival (healthy)
Thiba et al. 2007 [35]/Japan	32 GCP, 16 GAgP and 8 LAgP patients. *A.a.*-(+): LAgP (53%), GAgP (38%), CP (16%). Serotype c was detected in 50% of LAgP patients.	Serotype c is predominant *A.a.* serotype in Japanese LAgP patients.
Van der Reijden et al. 2008 [36]/ Indonesia	In 1994 subjects with *A.a.*-(+) serotype: b (53.7%), a (17.1%), c (14.6%), e (2.4%), multiple serotypes (12.2%); in 2002: a (7.5%), b (30.2), c (35.8%), e (9.4%), Multiple serotypes (17%). From 24 subjects who were positive serotypes both in 1994 & 2002: 14 (58.3%) had had the same serotype, 10 subjects (41.7%) with different serotype.	Subgingival presence of *A.a.*, but not a specific serotype is associated with a higher degree of inflammation. *A.a.* serotypes distribution in Indonesia young adults shifts from predominantly serotype b to a more equal prevalence of serotypes b and c.
Kim et al. 2009 [37]/ Korea/Germany	194 patients (96 Germans, 98 Koreans) with AgP or severe CP. Serotypes a through f were tested. *A.a.*-(+): Germans (27.0%,), Koreans (22.2%). In Germans: b (33.3%, c (25.0%), a (20.8%). In Koreans: c (61.9%), d (19.0%).	The distribution of *A.a.* serotypes may exhibit marked differences.
Kawamoto et al. 2009 [38]/Brazil	*A.a.* serotypes: c (68.0%), b: from AgP, high leukotoxin production. 57.1% of a serotype: low toxicity to Chinese hamster ovary (CHO) cells. Serotypes b and c were highly toxic strains.	Differences in prevalence of the low and highly cytotoxic strains among serotypes reinforce the hypothesis that serotype b and c isolates of *A.a.* are more virulent than serotype b strain.
Hoglund Aberg et al. 2009 [39]/Sweden	Serotypes a-c ad e, but not d or f, were detected from the 14 7 -9 yrs- old subjects at the baseline examination. Among the isolates from the 6 *A.a.* positive young adults, serotypes a-c, and f were identified.	The presence of *A.a.* and early bone loss in the primary dentition does not necessary predispose the individual to periodontal attachment loss in the permanent dentition.
Roman-Torres et al. 2010 [40]/Brazil	*A.a.* -(+): In 85/486 (17.5%) subjects, 68 were infected by at least 1 serotype, 7 by mixed, and 10 were non-serotyped. Serotypes d and f were not detected. Serotype c showed the highest prevalence (52.9%), followed by a (31.8%).	The prevalence of serotype c in severe periodontitis was significantly greater than that of serotypes of a and b.
Chen 2010 [41]/US	161 subjects to give 82 isolate. Serotypes: a (21, 25.6%), b (12, 14.6%), c (41, 50%), e (6, 7.3%), f (1, 1.2%), non-typed (1, 1.2%). 11/14 (78.6%) subjects were infected by a single serotype, 3/14 (21.3&) were infected by 2 serotypes.	Serotype c is the dominant *A.a.* serotype.
Takada et al. 2010 [42]/Japan	Serotype g of *A.a.* in a patient with periodontitis patient.	New serotype g was reported.
Skellart et al. 2011 [43]/Greece	No statistical differences were observed concerning the distribution of serotypes among groups. Serotype c was more pre-dominant within the periodontally diseased groups; no JP2 clone.	*A.a.* serotype b was not statistically correlated with periodontal disease.
Claesson et al. 2011 [44]/Sweden	JP2 clone (serotype b) was detected in samples from 2 of the family members.	Caucasian JP2 carriers exist and older subjects can carry the JP2 clone of *A.a.*.
Pinheiro et al. 2012 [45]/Brazil	26 *A.a.* isolates were classified into 6 serotypes(a -f).	Two serotype b (7.7%) from AgP patients, highly leukotoxic genotype; c is the most prevalent.
Cortelli et al. 2012 [46]/Brazil	204 subjects with-*A.a.*-(+): single serotype (152), variable infected (27), non-typed (25). Serotypes a, b, and c were largely found (%), and serotype c was the most prevalent, d-e-f were not detected or rare.	Serotype c was the most prevalent in both diseased and healthy subjects. AgP subjects were not exclusively associated with *A.a.* serotype b.

Jentsch et al. 2012 [47]/German	99 Subjects with *A.a.*-(+): a (25, 5.2%), b (22, 22.5%, including 2 with JP2), c (21, 21.2%), others and non-typed	Results show that *A.a.* serotype are different. between the cities and native and immigrants.
Bandhaya et al. 2012 [48]/Thialand	Serotype c (57%) was the most prevalent, followed by a (33%) and b (7%).	No significant relationship between serotypes and the extent or severity of periodontal disease.
Brigido et al. 2014 [49]/Review	12/85 studies met criteria: a, b, and c were largely found, c was the most prevalent.	Serotypes a, b, and c are globally dominant, serotypes d and e are rare, f is still unknown in distribution. Distribution pattern of *A.a.* vary among subjects of different ethnicity and geographic regions. The correlation of different serotypes with periodontal conditions remains unclear.
Tsuzukibashi 2014 [50]/Japan	Serotype g of *A.a.* gene cluster and primers for serotyping were reported.	The specific primers derived from these different areas are useful in identification and distribution of serotype g. among *A.a.* from clinical samples.
Minguez et al. 2014 [51]/Japan	40/701 (5.7%) subjects with *A.a.*-(+): b (30 subjects), co-colonization (7 subjects, most are a and b). Among 79 isolates: a (24), b (30), c(12), d (4), no JP2, 65.8% were cdt+.	The results show that the most common serotypes are a and b (b is the most prevalent in mono-colonization), e and f were not detected. All isolates (100%) are with genes responsible for the indication of leukotoxin.
Feng et al. 2015 [52]/China	62 AgP patients and 45 HC were analyzed.	Serotype c was the main serotype of *A.a.* in Chinese patients with AgP.
Pahumunto et al. 2015 [53]/Thailand	44 CP patients yield 79 strains of *A.a.* from deep pockets, 17 strains from shallow pockets. 84.1% of A.a.-positive: serotypes: a/18.2%, c/5.9%, e/9.1%, f/11.4%, no b and d, non- typed/45.5%. A JP2-like strain (530bp deletion, from 2 patients belong to serotype c) was found. 2 strains with 886bp insertion on the Itx promoter. Most patients showed only one serotype (32.4%), 29.7% showed 2 and 3 different serotypes.	A greater subtype diversity of *A.a.* predominated by non-typed strains than previously reported. Isolates with 530bp deletion or 886 insertion of the Itx promoter were serotyped as serotype c.
Minguez et al. 2016 [54]/Morocco	21/59 (35.6%) periodontitis patients were *A.a.*-positive. 39 *A.a.* isolates were b serotype only, 5 isolates from 2 patients (12.2% of the strains were JP2-leukotoxin positive, 78% were also cdt-positive.	*A.a,* can be frequently found in Morocco.
Joshi et al. 2017 [55]/India	Five serotypes: a (38.09%), 2 serotypes (36.5%), 3 serotypes (6.3%), 4 serotypes (4.7%), no JP2 strain. b (46.3%), c (36.5%) and e (38.09%) were the most serotypes. 11/63 subjects with positive CMV, 4/63 with positive- EBV, 9/63 with both viruses.	The presence of multiple serotypes and a combination of any serotype with herpesvirus is associated with greater severity of the disease.
Claesson et al. 2017 [56]/Sweden	Younger patients (</=35 yrs. old) were with higher *A.a.*-positive frequency, b serotype was more prevalent. JP2 in 1.2% (majority carriers were non-African origin).	For presence and characteristics of *A.a.* in clinical samples the age of the carriers were a discriminating factor. Non-African carriers of the JP2 genotype of *A.a.* were identified.
Setty et al. 2017 [57]/India	35/75 subjects (25 AgP, 25 CP, 25 HC), age from 14-55 yrs. old harbored *A.a.* (46.66%). Serotypes: c (19/35, 54.28%), b (non-alone), 2 samples were positive for both serotypes (b and c, 5.71%), non-typed (14, 40%).	Serotype c was predominant in periodontal disease as well as periodontal healthy individuals. Association could be present between genotypes serotype and genotype-periodontal status.
Liu et al. 2017 [58]/ Taiwan	One hundred subjects: c serotype (22%) and e (11%) were most common.	*A.a.* strains with different serotypes are widely distributed in a Taiwanese.

Akrivopoulou 2017 [59]/UK	Serotypes: a (48.6%), c (22%), b (2%), e (2%), mixed serotypes (12%), and not typed (7.14%).	Resistance serotypes of *A.a.* were demonstrated. Antimicrobial susceptibility investigation in patients with AgP prior to periodontal therapy.
Pietiannen et al. 2018 [60]/Finland	497 patients underwent coronary angiography. *A.a.*-positive: c (35.7%), b (28.6%), a (26.2%), e (7.1%), d (2.4%), f (0%).	Serotype-positive subjects had less teeth, higher BoP. Serotype b and c were associated with PPD and periodontal inflammatory-burden. Serotype c had the highest in saliva and subgingival bacterium quantities and serum antibody levels against *A.a.*. Serotypes b and c are the most frequent (59.3%) in coronary artery disease (CAD) patients associated with risk of stable CAD, also associated with the severity of CAD. The results suggest that *A.a.* serotypes b and c associate with periodontal and CAD status.

Discussion

It is convinced that the differences in serotypes distribution related to geography and/or ethnic group. The current presented data indicate that the geographic distribution of serotypes is not uniform [4,40,43,49]. The distribution pattern of *A.a.* serotypes varies greatly depending on the periodontal status of the allocated population and the country where the study takes place [30,32,35 ,40,43,45,47,49,52,53,58]. Some studies suggest that different *A.a.* serotypes are associated with periodontal health, periodontitis [6,10,15,18,31,34,39,49,52,57]. It is suggested that patients are usually infected by one serotype and colonization is stable over time [8,36,37], however occasional individuals are infected with two or three serotypes [34,37,39,40,44,47,52,545,57,59]. Most investigators found relatively low frequencies of multiple–serotype infection, except a study in Japan that shows 2 or 3 serotypes of *A.a.* with a frequency of 33% of the sites tested [31]. In general, the serotypes a-c occurred much more frequently among oral isolates than serotypes d-g. In African-Americans, a, b, and c serotypes seem to be distributed in equal frequencies, whereas in Hispanic subjects, a strong association with serotype c was reported [34]. In Greece [43], serotype a, b, and c were largely found to be equally distributed. In Brazilian population, the serotypes are in majority of a, b and c (up to 98%), with the serotype c most prevalent. Serotypes d, e, and f were either rare or not-detected [16,40,46]. In 2010 Chen et al. [41] reported that the serotype c is the dominant serotype followed by serotypes of a, and b, the d, e, and f were either not detected or relatively rare in the United States [41]. This is greatly different from the previous reported.

Almost all the studies showed that the Asian populations were commonly infected with *A.a.* serotype c, but occasionally colonized with serotype b [15,21,22,25-27,30,31,35-37,48,50-53,55,57,58]. In Taiwan, two studies demonstrated that the c serotype was the predominant [21,58], other studies found that serotype b was more than c or other serotypes [15,32]. In contrast, serotype b was commonly observed in Caucasian populations [37] and in German patients [37]. The serotype distribution pattern of *A.a.* within a local population may change over time, as seen in Indonesian periodontitis patients between 1994 to 2002 [36]. Serotypes d-f were rarely detected in most populations worldwide [40,42,45], however, a high prevalence of serotype e (19-47%) was noted in Indonesian [36] and Japanese [31]. *JP2* (serotype b) strain with super-leukotoxicity was discovered in 1979 by the authors of Tsai et al. [61]. In Japan, serotype c was predominantly identified in the gingival tissues of LAgP patients [31], and the distribution of serotypes was influenced by the presence of *P. gingivalis* (*P.g.*). The longitudinal follow-up study in Indonesia demonstrated that the mean increase in probing pocket depth between 1994 and 2002 was significantly greater in subjects' culture positive in 2002 in comparison to subjects without detectable *A. actinomycetemcomitans (A.a.)* in 2002 [36]. The shifts of the predominant serotype b to a more prevalence as evidenced by the studies in Indonesia and in the United States [41] might be explained to some extent, associated with the periodontal treatment including the use of antibiotics, and the high titer of antibody levels to predominant infected serotypes of *A.a.* The high levels of anti-*A.a.* antibody together with viable polymorphonuclear neutrophils (PMNs) and complement could more efficiently kill the infecting *A.a.* [62]. Thirdly, some previous studies classified serotype f as serotype b due to the serological cross-reactivity with anti-serotype b-specific antiserum [29]. Fourthly, study has shown that the recombination between strains of the same *A.a.* serotype appears to take place in nature, suggesting that non-serotypeable strains are serotype antigen-deficient variants originating from strains of the known serotypes [63]. In Brazil, AgP subjects were not exclusively associated with *A.a.* serotype b [40,46]. Isolates from healthy subjects belong to serotype c or a [46]. Serotype c was the most *A.a.*, and was isolated from various periodontal conditions, including AgP [45]. In Greek population, *A.a.* was more prevalent in untreated periodontitis subjects, but no clear predominance of a specific *A.a.* serotype and absence of the *JP2* clone were observed [43]. In Sweden, the findings indicate that periodontitis affecting the primary dentition does not necessary leads to the presence of periodontal attachment loss in the permanent dentition [39].

The *JP2* clone shows a limited geographical and ethnic host range, predisposing in subjects with an African lineage, but absent from non-African population from Northern Europe [14,65]. However, Claesson et al. [44] found that Caucasians can carry the *JP2* clone of *A. actinomycetemcomitans.* The studies cited in this review have varied widely in periodontal disease diagnosis and status, sampling protocols, study design and microbial detection methods and serotype analysis techniques. The periodontal therapy aims to the elimination of *A.a.* from periodontal pockets has been shown to be correlated with the outcomes of therapy. Akrivopoulou et al. [59] studied the prevalence of *A.a*. serotypes and reported

that of the 56 isolates tested, 100% were resistant to penicillin and metronidazole, 87.5% to clindamycin, 83.9% to amoxicillin and 76.8% to ceftazidime; low rates of resistance to tetracycline (8.9% resistant) and 2013; 5:20320. http//dx.dol.org/10.3402/jom. v510.20320. amoxicillin/clavulanic acid (14.3%); no isolates were resistant to ciprofloxacin.

In the study of the antibiotic resistance in human peri-implantitis microbiota, Ramus et al. [64] reported that all six *A.a.* subject strains exhibited *in vitro* resistance to clindamycin, and five to doxycycline, whereas none were resistant *in vitro* to either amoxicillin, metronidazole or amoxicillin plus metronidazole [65]. However, adjunctive systemic amoxicillin plus metronidazole medication to scaling and root planing (SRP) significantly improved the clinical outcomes with respect to mean probing pocket depth, clinical attachment loss compared to SRP alone [66]. In contrast, *Aggregatibacter actinomycetemcomitans JP2* homotypic biofilms were more susceptible *in vitro* to doxycycline than amoxicillin plus metronidazole [66]. Such results highlight the need for culture and antibiotic susceptibility tests in patients with aggressive periodontitis (AgP) and patients with peri-implantitis prior to systemic use of antibiotics concomitantly to periodontal therapy. In conclusion, this review indicates that different ethnic groups are preferentially colonized by different *A. actinimycetemcomitans* serotypes and the relationship between different *A.a*. serotypes and periodontal conditions remains to be investigated in the future.

Conflict of interest

The authors declare that they have no conflict of interests related to this publication.

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