Iraqi Journal of Market Research and Consumer Protection
(2025) 17(2): 146-156.
DOI:
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المجلة العراقية لبحوث السوق
وحماية المستهلك

EXPLORING STREPTOCOCCAL MICROBIOTA AS POTENTIAL INDICATORS FOR PROGRESSION OF PERIODONTAL DISEASES

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Received 24/ 9/ 2023, Accepted 26/ 10/ 2023, Published 30/ 9/ 2025

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ABSTRACT

A disturbance in the equilibrium of oral microbiota may represent a leading cause of poor oral hygiene. Dysbiosis of the microbiota is the main cause of inflammatory illnesses, known as periodontitis. Communication between *Streptococcus* spp. and other oral bacteria could be relevant, and therefore, indicators of different forms of periodontitis. The current study aimed to investigate the association between certain *Streptococcus* spp. with poor oral health and developing periodontal disorders. A total of 166 samples were collected from individuals attending Ghazi Al-Hariri Hospital for Surgical Specialties and Specialized Dental Centers in Baghdad, Iraq. *S. mutans, S. sanguis, S. thoraltensis, S. infantarius, Aggregatibacter actinomycetemcomitans, Bifidobacterium* spp. have been surveyed and identified in 166 individuals using VITEK 2 system. The results approved that the *Streptococcus* spp. colonisation have strong significant correlations with a certain periodontal disease alongside its relationship with other bacterial species. Mainly, infectious *Streptococcus sanguis* is significantly associated with gingivitis (rho = 0.239, *p*= 0.002), but inversely corelated with acute periodontitis (rho= -0.165*, *p*= 0.034). Moreover, *Streptococcus mutans is* inversely associated with the chronic periodontitis (rho= -0.155*, *p*= 0.046) and significantly with dental caries & pulpitis (rho= 0.252**, *p*= 0.001). *Streptococcus infantarius* significantly correlates with chronic periodontitis (rho = -0.183*, *p*= 0.018) and inversely associated with the oral hygiene status. The findings indicate that streptococcal microbiota act as potential indicators for developing a range of periodontal diseases forms. However, the aggressive periodontitis was associated with *Aggregatibacter actinomycetemcomitans*. The findings suggest that further investigation of molecular oral microbiome is required to uncover their potency to develop the severity of oral diseases.**

Keywords: Dysbiosis, Oral Diseases, Periodontitis, Oral Hygiene, *Streptococcus thoraltensis*.

استكشاف الكائنات الحية الدقيقة العقدية كمؤشرات محتملة لتطور أمراض اللثة

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الخلاصة

قد يمثل اضطراب توازن الكائنات الحية الدقيقة في الفم سببًا رئيسيًا لضعف نظافة الفم. اختلال الميكروبيوم هو المصدر الرئيسي للأمراض الالتهابية المعروفة باسم التهاب اللثة. الارتباط بين *Streptococcus* spp. وغيرها من البكتيريا الفموية يمكن أن تكون ذات صلة، وبالتالي، مؤشرات لأشكال مختلفة من التهاب اللثة. هدفت الدراسة الحالية إلى التحقق من العلاقة بين بعض أنواع المكورات العقدية *Streptococcus* spp. مع ضعف صحة الفم وتطور اضطرابات

اللثة. تم جمع 166 عينة من الأفراد المراجعين لمستشفى غازي الحريري للتخصصات الجراحية ومراكز طب الأسنان المتخصصة في بغداد، العراق. تم عزل وتشخيص *S. mutans*، *S. sanguis*، *S. thoraltensis*، *S. Infantarius*، *Aggregatibacter actinomycetemcomitans*، *Bifidobacterium* spp. في 166 فردًا باستخدام نظام VITEK 2. أثبتت النتائج أن بكتريا *Streptococcus* spp. تملك ارتباطات مهمة قوية مع بعض أمراض اللثة إلى جانب علاقتها بأنواع بكتيرية أخرى. بشكل رئيسي، ترتبط *Streptococcus sanguis* المعدية بشكل كبير بالتهاب اللثة (rho = 0.239، p = 0.002)، ولكنها ترتبط عكسيًا بالتهاب اللثة الحاد (* rho = -0.165، p = 0.034). علاوة على ذلك، ترتبط *Streptococcus mutans* بشكل عكسي بالتهاب اللثة المزمن (*Rho= -0.155، p=0.046) وبشكل ملحوظ مع تسوس الأسنان والتهاب لب السن (**rho= 0.252، p=0.001). ترتبط *Streptococcus infantarius* بشكل كبير بالتهاب اللثة المزمن (*Rho = -0.183، p= 0.018) وترتبط عكسيًا بحالة نظافة الفم. تشير النتائج إلى أن الكائنات الحية الدقيقة العقدية تعمل كمؤشرات محتملة لتطوير مجموعة من أشكال أمراض اللثة. ومع ذلك، كان التهاب اللثة العدواني مرتبطًا ببكتيريا *Aggregatibacter actinomycetemcomitans*. تشير النتائج إلى أن هناك حاجة إلى مزيد من البحث في الميكروبيوم الجزيئي عن طريق الفم للكشف عن مدى فعاليته في تطوير شدة أمراض الفم.**

الكلمات المفتاحية: اختلال الميكروبيوم، أمراض الفم، التهاب اللثة، نظافة الفم، العقدية الصدرية.

INTRODUCTION

Oral tissues and structures have a heterogeneous nature, providing a complex and diverse ecological habitat for all microorganisms that reside in various niches within the oral cavity **(Li *et al*., 2022)**. In the Human Microbiome Project (HMP), Ten diverse habitats of the mouth have been surveyed in the Human Microbiome Project to understand the relationship between bacterial microbiota and the oral cavity environment **(Segata *et al*., 2012)**. Despite the potential for colonization on any surface within the mouth, the HMP chose locations that indicated a variety of habitat types. Because different environmental factors, might result in different microhabitats, none of these locations are homogeneous **(Welch *et al*., 2020)**.

However, the bacterial flora residing within the mouth is actively involved in maintenance of oral health balance **(Gaonkar *et al*., 2018)**. Therefore, the breakdown of host-microbe equilibrium results in a microbial shift in the biofilm and a decline in the proportion of symbionts and/ or an increase in the proportion of pathobionts **(Jiao *et al*., 2013; Hajishengallis & Lamont, 2016)**. *Streptococcus* was the most predominant genus in the oral microbiota. Commensal bacterial species are known to compete for nutritional supply and receptor sites with all the exogenous microbes, thus making them an essential part of host immunity **(Brown & Whiteley, 2007)**.

Oral environmental stress can disrupt the homeostatic balance of microbial habitats **(Hong *et al*., 2019)**. Dysbiotic microbiota represent a source for the inflammatory events leading to periodontitis **(Van Dyke *et al*., 2020)**. Microbial shifting from the main symbiotic bacteria "symbionts" to dysbiosis, with high proportions of pathogenic bacteria "pathobionts" is linked to the transition from periodontal health to the severe stages of periodontitis. Numerous stresses, such as the host immune-inflammatory response, individual sensitivity, and behavioural risk factors like smoking, have an impact on this shift **(Abdulkareem *et al*., 2023)**. Gingivitis, the most common form of periodontal disease that represents an inflammation of the gingiva by the accumulation of dental plaque, or bacteria and debris between the gum line and teeth, affects up to 90% of population **(Pihlstrom *et al*., 2005)**. When oral hygiene is improved, the reactive condition of gingivitis can be reversed. Periodontitis is a persistent, damaging, and permanent inflammatory status that follow gingivitis consequences causing advanced forms (aggressive or chronic) of periodontitis **(Kinane *et al*., 2017)**. In such cases, the oral pathogens can surround periodontium and enter the tissues more deeply leading to host defence activity against the invasive bacteria. However, the host defences cause periodontium destruction as a result of the defence process against the bacteria **(Highfield, 2009)**. The connective tissue and alveolar bone supporting the tooth are destroyed as a result of the host reaction occurred by the polymicrobial community change **(Paster *et al*., 2001)**.

Previous reports have identified oral streptococci are a typical component of the human oral microbiota, mainly the species; *S. mutans*, *S. salivarius*, *S. sanguis*, *S. mitis*, *S. oralis*, *S. pyogenes*, and *S. infantarius* that have been identified in various regions of the oral cavity, including the tooth surfaces, epithelium and saliva **(Takada *et al*., 2010)**. Among a peculiar group of streptococci, *S. thoraltensis* was reported for the first time to be the main colonizing isolate in the oropharynx and nasal cavity of 29 fuel workers in Saudi Arabia **(AlWakeel, 2017)**. These workers do not relate to the type of bacteria that cause the infection with the type of diseases that form in the oral cavity but were initially assessed to investigate the effects of fuel products exposure on the bacterial colonisation in their upper respiratory tract by conducting a cross-sectional study. Since the streptococcal microbiota represents the main oral bacteria that implicate in dental dysbiosis, we hypothesised that these bacteria could be a potential indicator for predicting the dental illnesses that affect oral health. Therefore, the aim of the current study is to explore the association between certain *Streptococcus* spp. with poor oral health and developing periodontal disorders.

MATERIALS AND METHODS

Patients and clinical data:

A total of 166 specimens were collected from individuals attending Ghazi Al-Hariri Hospital for Surgical Specialties and Specialized Dental Centers in Baghdad, Iraq. Samples were collected during the period from September 2021 to February 2022. Samples were collected according to different parameters age, gender, sample type (saliva, supragingival plaque, subgingival plaque, caries, GCF and sputum), periodontal diseases, smoking status, alcohol consumption, oral hygiene, and health status of recruited individuals. This study was approved by College of Science Research Ethics Committee at the University of Baghdad under the reference number (CSEC/0122/0013). Written informed consent was obtained from all participants and all methods in this study were performed in accordance with the relevant guidelines and regulations. The exclusion criteria were considered for patients with current antibiotic treatment or antibiotic treatment within the last 4 weeks or using of antiseptic mouthwashes. The aforementioned 4 weeks period represent the maximum duration of using antiseptic mouthwashes including antibiotics that significantly reduce the oral bacterial populations **(Putt *et al*., 1996; Vanishree *et al*., 2021)**. Therefore, the non-treated patient with the above period were chosen in our study to eliminate the effect of the antibacterial agents.

Microbial sample collection:

According to technical requirements, all specimens were collected into a transport medium, moved within a maximum of 4 hours to the microbiological laboratory, and cultivated both aerobically and anaerobically within 24 hours after collection.

Bacterial Isolation and Identification:

Oral *Streptococcus spp*. including *S. thoraltensis* were isolated from collected samples by incubating at 37 °C, 5-10% CO_2 for 72 hours on Mitis Salivarius Bacitracin (MSB) agar (C*at. no*.: M259-500G - *HIMEDIA*, India). The MSB agar was prepared by adding 54 g of mitis salivarius agar and 90 g of sucrose to 600 ml of distilled water. 700 mL of a 1% tellurite and 700 ml of a 3 mg/ml bacitracin were added when the temperature reached 50°C after autoclaving sterilization **(Zeng *et al*., 2020)**. Biochemical characteristics were further identified using VITEK 2 system (bioMérieux).

Statistical analysis:

Statistical evaluation was performed using χ^2 test *to examine* categorical variables, while *spearman test was conducted to inspect the correlation between variables at 2-tailed levels alongside its rho coefficient*. *P* values <0.05 were considered to indicate a statistically significant difference. All statistical tests were conducted using IBM® SPSS® statistical software (Version 28; IBM SPSS, Armonk, NY, USA).

RESULTS

Prevalent types of dental diseases

The data of overall bacterial survey in the current study manifested that the highest proportion of dental disorders represents gingivitis (34.4%, n=57) of the cases, followed by almost similar rates of periodontitis forms; acute (25.9%, n=43) and chronic (24.7%, n=41). while the lowest rate of the diseases is the aggressive form of periodontitis (1.2%, n=2). to the highest one. On the other hand, those with dental erosion recorded (3%, n=5) over the total examined the cases (Figure 1).

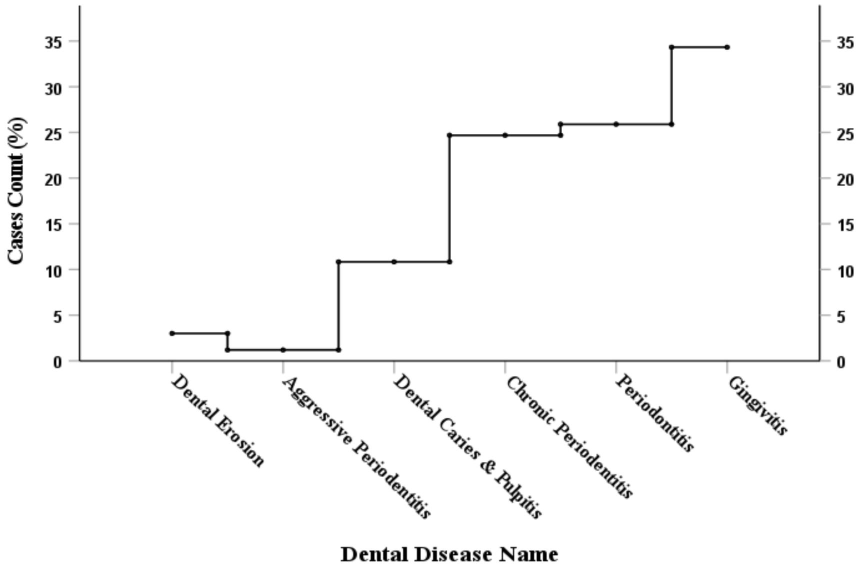

Figure (1): A line graph demonstrating the proportions of the most prevalent types of dental diseases affected the studied individuals ranged from the lowest type (Aggressive Periodontitis) to the highest one (Gingivitis).

Proportional population of oral streptococci

Regarding the oral microbiota, the results of the bacterial diagnosis showed that, nine *Streptococcus* spp. were dominant in the analysed dental samples, accounting for 5.1% (n=18) *S. mutans*, 4.0% (n=14) *S. salivarius*, 3.4% (n=12) *S. sanguis*, 2.8% (n=10) *S. mitis*, 2.8% (n= 10) *S. oralis*, 1.1% (n= 4) *S. pyogenes*, 1.1% (n= 4) *S. thoraltensis*, 1.1% (n= 4) *S. infantarius* and 1.7% (n= 6) *Streptococcus* other spp. are being the most prevalent bacteria (Figure 2).

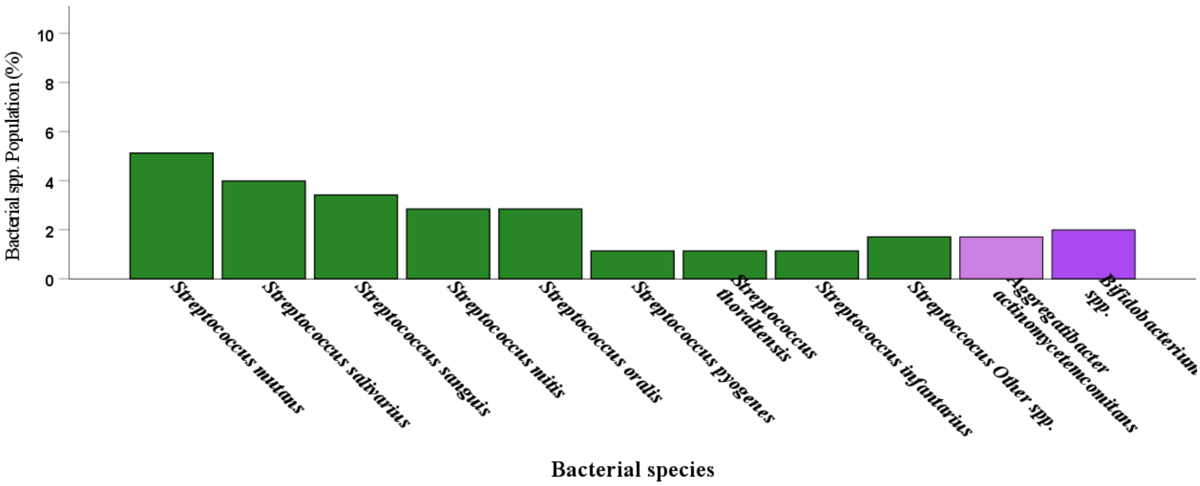

Figure (2): A bar chart showing the percentages of *Streptococcus* bacterial species diagnosed in the investigated oral specimens.

The cultural results showed that *S. thoraltensis* colonies have grown as a rounded smooth black shape after applying the anaerobic growth conditions mentioned above (Figure 3).

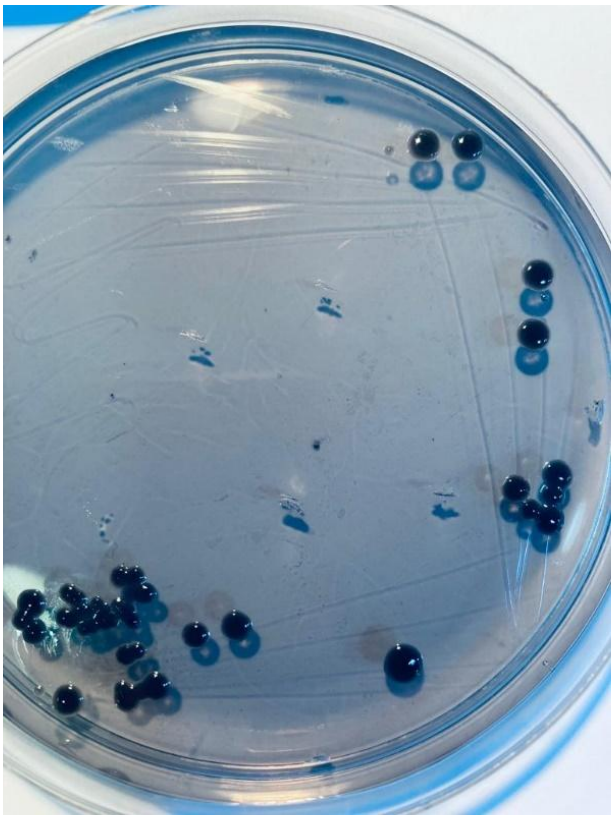

Figure (3): A representative image depicts growing colonies of *Streptococcus thoraltensis* of its selective culture on Mitis Salivarius agar.

Three isolates of *S. thoraltensis* have been succefuly identified by VITEK 2 system with probabilities of 89-93% (Figure 4).

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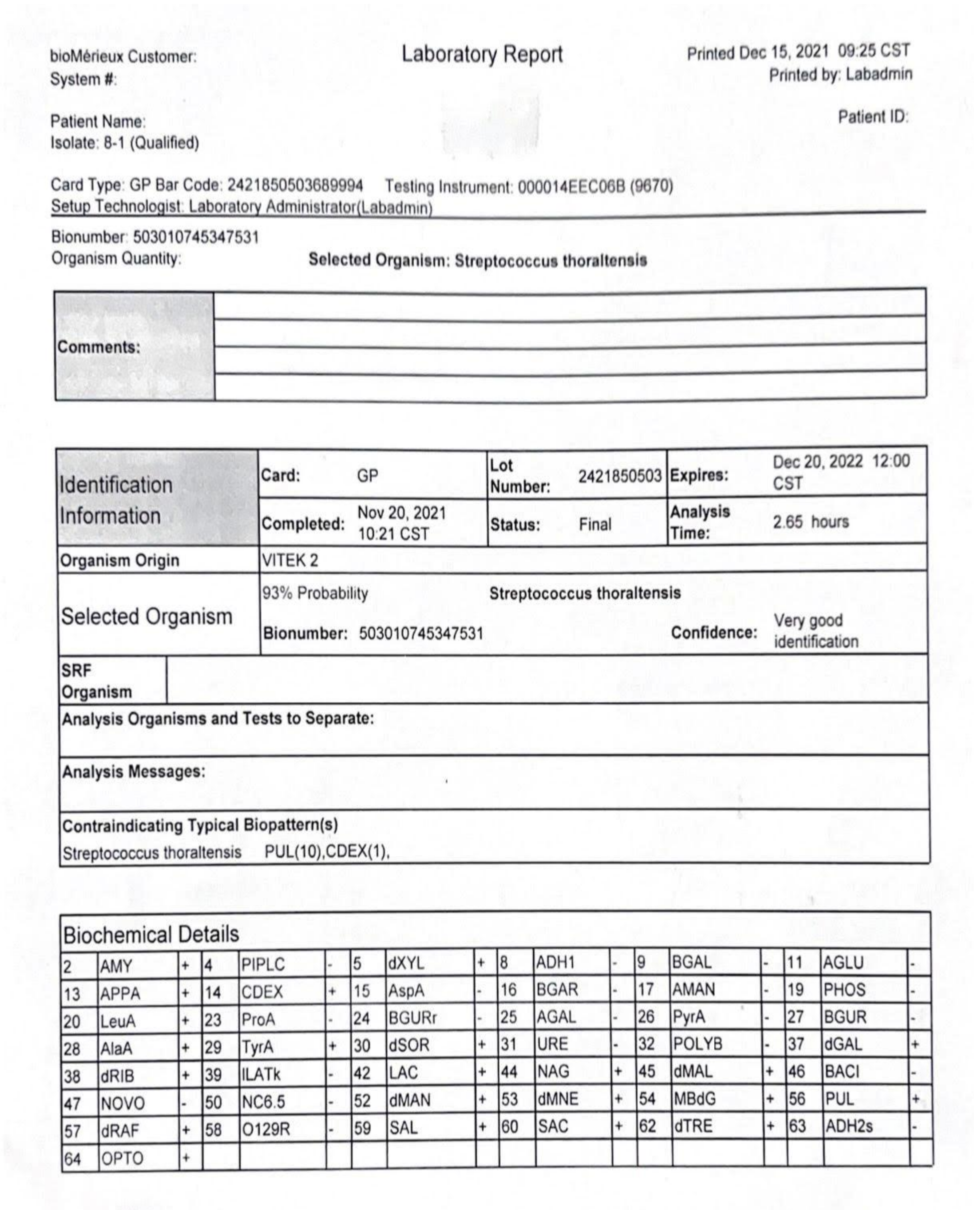

bioMérieux Customer:
System #:

Laboratory Report

Printed Dec 15, 2021 09:25 CST
Printed by: Labadmin

Patient Name:
Isolate: 8-1 (Qualified)

Patient ID:

Card Type: GP Bar Code: 2421850503689994 Testing Instrument: 000014EEC06B (9670)
Setup Technologist: Laboratory Administrator(Labadmin)

Bionumber: 503010745347531
Organism Quantity:

Selected Organism: Streptococcus thoraltensis

Comments:

Identification Information	**Card:**	GP	**Lot Number:** 2421850503	**Expires:**	Dec 20, 2022 12:00 CST	
	Completed:	Nov 20, 2021 10:21 CST	**Status:** Final	**Analysis Time:**	2.65 hours	
Organism Origin	VITEK 2					
Selected Organism	93% Probability		**Streptococcus thoraltensis**			
	Bionumber: 503010745347531			**Confidence:**	Very good identification	
SRF Organism						
Analysis Organisms and Tests to Separate:						
Analysis Messages:						
Contraindicating Typical Biopattern(s)						
Streptococcus thoraltensis PUL(10),CDEX(1),						

Biochemical Details

2	AMY	+	4	PIPLC	-	5	dXYL	+	8	ADH1	-	9	BGAL	-	11	AGLU	-
13	APPA	+	14	CDEX	+	15	AspA	-	16	BGAR	-	17	AMAN	-	19	PHOS	-
20	LeuA	+	23	ProA	-	24	BGURr	-	25	AGAL	-	26	PyrA	-	27	BGUR	-
28	AlaA	+	29	TyrA	+	30	dSOR	+	31	URE	-	32	POLYB	-	37	dGAL	+
38	dRIB	+	39	ILATk	-	42	LAC	+	44	NAG	+	45	dMAL	+	46	BACI	-
47	NOVO	-	50	NC6.5	-	52	dMAN	+	53	dMNE	+	54	MBdG	+	56	PUL	+
57	dRAF	+	58	O129R	-	59	SAL	+	60	SAC	+	62	dTRE	+	63	ADH2s	-
64	OPTO	+															

Figure (4): A chart illustrate *Streptococcus thoraltensis* identification using VITEK 2 compact system at 93% probability.

Our results demonstrate strong significant correlation with the disease aggressiveness (rho = 0.274, p <0.001). Moreover, our analysis approved that *A. actinomycetemcomitans* is inversely associated with oral hygiene status (rho = -0.192, p = 0.013) (Table 1). The most likely cause of aggressive periodontitis was long believed to be *A. actinomycetemcomitans*. On the other hand, our data analysis reveals that *Streptococcus thoraltensis* is substantially connected with dental erosion (rho = 0.202**, p=0.009). This could account for the spotting of the species in patients 126 (75.9%) and healthy individuals 40 (24.1%) in both of our findings above.

Relationship between the oral bacteria and dental diseases progression

In terms of other *Streptococcus* spp., the current study demonstrates significant correlations between the tested streptococcal bacteria and the dental diseases. While *Streptococcus sanguis* infection is significantly associated with gingivitis (rho = 0.239**, *p*= 0.002), it was inversely correlated with acute periodontitis (rho= -0.165*, *p*= 0.034). Moreover, *Streptococcus mutans is* inversely associated with the chronic periodontitis (rho= -0.155*, *p*= 0.046) and significantly with dental caries and pulpitis (rho= 0.252**, *p*= 0.001). *Streptococcus infantarius* significantly correlates with chronic periodontitis (rho = 0.183*, *p*= 0.018) and inversely associated with the oral hygiene status. Therefore, Streptococcal bacterial seem to deeply implicate in developing dental disorders.

Table (1): Statistical analysis chart illustrates the correlations between the tested oral bacteria and six types of the examined dental diseases alongside the oral hygiene status of the studied individuals (n=166).

Dental Disease	Spearman's test	*Streptococcus mutans*	*Streptococcus sanguis*	*Streptococcus thoraltensis*	*Streptococcus infantarius*	*Aggregatibacter actinomycetemcomitans*
Aggressive periodontitis	Correlation Coefficient (***ρ***)	-0.039	-0.031	-0.017	-0.017	**0.274****
	2-tailed Significant (**p val**.)	0.622	0.693	0.824	0.824	**<.001**
Chronic periodontitis	Correlation Coefficient (***ρ***)	**-0.155***	-0.106	-0.09	**0.183***	-0.036
	2-tailed Significant (**p val**.)	**0.046**	0.174	0.249	**0.018**	0.645
Dental caries & pulpitis	Correlation Coefficient (***ρ***)	**0.252****	0.052	0.072	-0.055	-0.068
	2-tailed Significant (**p val**.)	**0.001**	0.504	0.36	0.483	0.387
Dental erosion	Correlation Coefficient (***ρ***)	0.052	-0.049	**0.202****	-0.028	-0.034
	2-tailed Significant (**p val**.)	0.507	0.529	**0.009**	0.723	0.662
Gingivitis	Correlation Coefficient (***ρ***)	-0.007	**0.239****	-0.031	-0.031	-0.004
	2-tailed Significant (**p val**.)	0.925	**0.002**	0.693	0.693	0.958
Acute periodontitis	Correlation Coefficient (***ρ***)	-0.029	**-0.165***	-0.003	-0.093	0.033
	2-tailed Significant (**p val**.)	0.708	**0.034**	0.967	0.234	0.674
	Number (**Sample size**)	166	166	166	166	166
Healthy Oral Status	Correlation Coefficient (***ρ***)	0.086	0.069	0.145	-0.136	**-0.192***
	2-tailed Significant (**p val**.)	0.272	0.379	0.063	0.081	**0.013**
	Number (**Sample size**)	166	166	166	166	166

****** Correlation is significant at the 0.01 level (2-tailed).
***** Correlation is significant at the 0.05 level (2-tailed).
ρ: rho

The study revealed a significant correlation between the individuals age and the microbiota of *Bifidobacterium* (rho = .155*, *p*= 0.047), *Porphyromonas gingivalis* (rho = .192*, *p*= 0.013), and *Candida albicans* (rho = .190*, *p*= 0.014). On the other hand, the age was inversely correlated with *Streptococcus sanguis* (rho = -.153*, *p*= 0.05), *Citrobacter freundii* (rho = -.167*, *p*= 0.032), and *Enterococcus* spp. (rho = -.158*, *p*= 0.042). However, no significant correlation was shown with the gender.

DISCUSSION

The variety of dental diseases emerged among the examined individuals in the current study suggests that there is unmet clinical need for an effective oral hygiene practice. Consequently, it may indicate that increasing oral infections spread may affect quality of life. It has been reported that individuals with periodontal disorders frequently undergo dysbiosis in the composition of the oral microbial biofilm, including greater abundances of particular phylotypes **(Marchesan *et al*., 2016; Paes Batista da Silva *et al*., 2016)**. The presence of *Streptococcus* spp. throughout the early stages of periodontal diseases seems to be consistent across patients and may serve as an early-stage microbial indicator for poor oral hygiene and developing periodontitis **(Palmer Jr *et al*., 2017)**.

In fact, *S. thoraltensis* was previously reported in a number of studies in non-oral samples **(Takada *et al*., 2010; Petridis *et al*., 2018; Hai *et al*., 2020)**. However, it was only reported by **(AlWakeel, 2017)** from oral samples and our study represents the second report for diagnosing these bacteria. To the best of our knowledge that the unique growth morphology of *S. thoraltensis* presented in the current study has been reported for the first time in Iraq.

The colonization of *Aggregatibacter actinomycetemcomitans* in adolescents and young adults is strongly correlated with aggressive forms of periodontitis **(Henderson *et al*., 2010).** The most likely cause of aggressive periodontitis was long believed to be *A. actinomycetemcomitans*. However, it is now believed to be either a small periodontium-dwelling resident of the oral microbiota or, in some people, an opportunistic pathogen **(Tomita *et al*., 2013)**. This bacterial species has been found in oral regions with poor levels of hygiene **(Jiao *et al*., 2013)**, and it is well known for its capacity to form persistent biofilms that may cling to both abiotic and biotic surfaces (Schreiner et al., 2003). It is important to note that Petridis *et al.* **(Petridis *et al*., 2018)** were the first to record a case of bacteremia brought on by an infection with *S. thoraltensis* as a contributing factor in a human fever with no known cause. Our findings are intriguing in that they demonstrate that *S. thoraltensis* is one of the most common oral pathogens identified in patients with gingivitis and periodontitis and may have a role in the onset of these oral diseases.

CONCLUSION

Streptococcal microbiota represent potential indicator for determining the dental diseases, mainly (*S. mutans* and *S. sanguis*). Interestingly, *A. actinomycetemcomitans* bacteria have strong significant corelation with aggressive periodontitis, in addition to inverse corelation with healthy oral status. This association could be employed as potential risk factors for indicating the aggressiveness of periodontal diseases alongside poor oral hygiene. Further investigation of the oral microbiome is crucial to explore their potency for predicting other dreadful oral diseases such as head and neck malignancies on molecular bases. In addition, further investigation of oral microbial biofilm effects on developing periodontal diseases are requested in future studies.

ACKNOWLEDGMENTS

The authors would like to acknowledge Dr. Sabah Abdulaziz Issa consultant of Oral and Maxillofacial Surgery, Head of a Maxillofacial Center in Alshaheed Ghazi Al-Hariri Hospital for Surgical Specialties, Baghdad, Iraq, and Dr. Mohammed Shawket Attiya, Dental Hospital, Dijlah University College, Baghdad, Iraq, for facilitating the official process of accessing the oral patients to perform this research.

Conflicts of Interest
The authors declare no conflicts of interest.

Funding Statement: This research received no external funding.

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