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Article

Oral carriage of *Staphylococcus aureus* in people with different body mass index.

Colonización oral por *Staphylococcus aureus* en personas con diferente índice de masa corporal.

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Abstract: Background: The association between obesity and the oral microbiome has received great attention. **Objective:** This study aimed to determine the association of oral *Staphylococcus aureus* with different body mass index people. **Material and Methods:** A total of 155 saliva samples were collected. The individuals were grouped into three categories according to their BMI, normal weight, overweight and obese individuals. A loopful of saliva sample was cultured and incubated at 37°C for 24. *Staphylococcus aureus* isolates were diagnosed by colony characteristics, morphology, and biochemical tests. **Results:** The oral carriage rate of *Staphylococcus aureus* was 61.3% (65.1% females and 56.5% males). The *Staphylococcus aureus* rate was 68% in married and 60% in single people. The differences of oral carriage rates of *Staphylococcus aureus* in obese (73.6%) and overweight (85.4%) populations was statistically significant ($p<0.0001$) compared to the rate in normal weight group (34%). Among males, the highest oral carriage rate of *Staphylococcus aureus* was in overweight individuals (82.6%). Likewise, in females, the highest rate of salivary *Staphylococcus aureus* was among the overweight group (88.9%). Regarding marital status, in single people, the differences of *Staphylococcus aureus* in obese ($p=0.0003$) and overweight ($p<0.0001$) people was significantly compared to normal weight people. But, in married people, the differences in *Staphylococcus aureus* rates among all groups were statistically not significant ($p=0.0935$). **Conclusion:** *Staphylococcus aureus* was significantly related to overweight and obese individuals. The human oral *Staphylococcus aureus* may play a key role in the manifestation of obesity. The oral microbiota could provide a new target for improving the physical well being of humans.

Keywords: *Staphylococcus aureus; microbiota; mouth; body mass index; obesity; Iraq.*

Resumen: Antecedentes: la asociación entre la obesidad y el microbioma oral ha recibido gran atención. **Objetivo:** Este estudio tuvo como objetivo determinar la asociación de *Staphylococcus aureus* oral en personas con diferentes índices de masa corporal. **Material y Métodos:** Se recolectaron un total de 155 muestras de saliva. Los individuos fueron agrupados en tres categorías según su indice de masa corporal: normopeso, sobrepeso y obesos. Se cultivó un asa de muestra de saliva y se incubó a 37°C durante 24 horas. Los aislamientos de *Staphylococcus aureus*

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se identificaron mediante las características de la colonia, la morfología y las pruebas bioquímicas. **Resultados:** La tasa de colonización oral por *Staphylococcus aureus* fue del 61,3% (65,1% mujeres y 56,5% hombres). La tasa de colonización por *Staphylococcus aureus* fue del 68% en casados y del 60% en solteros. Las diferencias de las tasas de portación oral de *Staphylococcus aureus* en las poblaciones obesas (73,6%) y con sobrepeso (85,4%) fueron estadísticamente significativas (p<0,0001) en comparación con la tasa en el grupo de peso normal (34.0%). Entre los hombres, la tasa más alta de portadores orales de *Staphylococcus aureus* fue en individuos con sobrepeso (82,6%). En las mujeres, la tasa más alta de *Staphylococcus aureus* salival se también se presentó en el grupo con sobrepeso (88,9 %). En cuanto al estado civil, en solteros, las diferencias de *Staphylococcus aureus* en obesos (p=0,0003) y con sobrepeso (p<0,0001) fueron significativas compararadas con normopeso. Pero, en personas casadas, las diferencias en las tasas de *Staphylococcus aureus* entre todos los grupos no fueron estadísticamente significativas (p=0,0935). **Conclusion:** *Staphylococcus aureus* salival se relacionó significativamente en individuos con sobrepeso y obesidad. El *Staphylococcus aureus* oral humano puede jugar un papel clave en la manifestación de la obesidad. La microbiota oral podría proporcionar una nueva diana para mejorar el estado físico de los humanos.

Palabras Clave: *Staphylococcus aureus; microbiota; boca; índice de masa corporal; obesidad; Irak*

INTRODUCTION.

Obesity is considered one of the greatest health risks in today's societies and is estimated to be prevalent in more than 30% of the world's population.[1] Obese people have higher annual health care and medication costs compared to people of normal weight.[2] Epidemiological studies have mentioned potential environmental exposures, including diet, sedentary lifestyle, chronic inflammation, and microbiome status, as increasing the risk of obesity.[3] The interaction between genetics and the environment is the most important factor contributing to obesity as well as is the result of complex pathological adaptations of body cells.[4] Among these, the microbiome has received great attention since the previous decade.[5]

Researches on human gut microbiota have showed that the alteration in the ratio of Firmicutes to Bacteroidetes (F/B) has been associated with obesity and its metabolic disorders.[6] Several studies have shown differences in the occurrence of the composition of the oral microbiome in obese people.[7] It has been found that the salivary microbiome had a higher phylogenetic diversity in individuals with obesity.[8,9] Studies have reported that between 94% and 100% of healthy adults had oral colonization of *Staphylococcus spp*, from which 24% to 36% is characterized by the oral carriage of *Staphylococcus aureus*.[10] Oral infections by *Staphylococcus aureus* may lead to conditions such as endodontic infections, osteomyelitis, gastroenteritis, the formation of an abscess, septicemia, and pneumonia.[11,12] Of further concern, the oropharynx is often colonized with methicillin-resistant strains (MRSA), which can be difficult to kill.[13-15] The composition of commensal organisms at different body sites can differ between obese and normal weight individuals, which could affect the pathogenicity of these organisms.[16] Obesity is often associated with *Staphylococcus aureus* nasal colonization.[17]

National Health and Nutrition Examination Survey, interestingly, reported that obesity is associated with higher nasal prevalence *Staphylococcus aureus* in both men and women.[18] Studies revealed that there was a positive association between high body mass index (BMI) values and nasal carriage *Staphylococcus aureus*.[19] Also, a higher occurrence of S. aureus has been recorded in the saliva of obese women compared with a control group.[20,21] So far, there are limited data on this issue in the Kurdistan region, Iraq. The objective of this study was to investigate the differences in the composition of *Staphylococcus aureus* between obese, overweight and normal weight people in Duhok city, Kurdistan region, Iraq by using culture methods

MATERIALS AND METHODS.

Study setting and design

This cross-sectional study was conducted between November 2018 and June 2019. A total of 155 saliva samples were collected randomly from healthy adult university students. Samples were collected from both genders (86 females and 69 males) aged between 19-35 years. Information related to these patients such as gender, age, marital status, weight, height, was obtained.

Body Mass Index (BMI)

The Body Mass Index (BMI) of all participants was calculated according to the WHO guidelines.[22] The individuals were grouped into three categories according to their BMI, normal-weight individuals (BMI between 18.5 kg/m^2 and 24.9 kg/m^2), overweight individuals (BMI between 25.0 kg/m^2 and 29.9 kg/m^2) and obese individuals (BMI ≥30.0 kg/m^2).

Exclusion criteria

The exclusion criteria involved: the existence of any systemic disease, use of medications, smoking, pregnancy/lactation, using antibiotics (in the last three months), any chronic disease such as psychiatric disorders, anorexia, acute relapse, etc. Also, insufficient quantity (<2 mL) saliva samples were excluded.

Samples collection

Saliva samples were collected under sterile conditions based on a previous study by Wu *et al*.[9] Unstimulated whole saliva was collected from participants with an absence of severe periodontal destruction in the morning, between 9:00 am and 12:00 pm, in a dedicated area in Duhok city. Before taking the sample, the participant was asked to refrain from drinking, eating, and tooth brushing one hour before sampling. The mouth was rinsed with water to remove any food residue. After 10 minutes, about 5 ml of saliva was spat into a 50 mL DNA-free sterile container labelled with an identification number, age, gender, date and time of collection. The collected samples were transported to the microbiology laboratory within 1 hour, where the samples further processed.[9]

Isolation and identification of *Staphylococcus aureus*

A loopful of the collected saliva sample was inoculated on enrichment blood agar (LabM – UK), and selective and differential mannitol salt agar (LabM – UK), and incubated aerobically at 37°C for 24 hr. The identification of *Staphylococcus aureus* isolates was performed under standards and guidelines as follows: For isolation and identification, initially, the bacterial colonies were classified by Gram staining of bacterial colonies, and then the bacteria were identified based on colony characteristics (mannitol salt agar fermentation), morphology, and biochemical tests including catalase test and coagulase test.[27,28]

Statistical analysis

All statistical analysis of the recorded data was performed using the Minitab 18 software. A Chi-square test was used and the differences among variables were considered significant at a *p*-value of <0.05.

Ethics Statement

Verbal informed consent was obtained from all volunteers. The research design and methodology were approved by the scientific committee of the department of biology, college of sciences, University of Duhok, Kurdistan Region, Iraq

RESULTS.

A total of 155 individuals (69 males and 86 females) were recruited in the current study. Saliva samples of all participants were cultured and S. aureus was identified. In general, the oral carriage rate of *Staphylococcus aureus* was 61.3% (95/155).

Regarding gender, the oral carriage rate of *Staphylococcus aureus* in the female population (65.1%; 56/86) was higher than the rate in the males population (56.5%; 39/69), and this difference was statistically not significant (p=0.2749).

BMI for all 155 individuals was calculated and people were categorized into three groups: 53 obese individuals with BMI (≥30 kg/m^2); 41 overweight individuals with BMI (between 25.0 and 29.9 kg/m^2); 61 normal-weight individuals (control) with BMI (between 18.5 and 24.9 kg/m^2). Out of 53 obese individuals, 39/53 (73.6%) were positive for

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Staphylococcus aureus In overweight subjects, 35/41 (85.4%) carried *Staphylococcus aureus* Whereas, the carriage rate of oral *Staphylococcus aureus* in the normal weight (control) group was 34% (21/61).

The frequency of *Staphylococcus aureus* in obese and overweight groups was higher compared to the rate in normal weight group and these differences were statistically significant (p<0.0001), (Table 1). In males, the oral carriage rates of oral *Staphylococcus aureus* in obese, overweight and normal weight individuals were 64.7% (11/17), 82.6% (19/23) and 31% (9/29) respectively.

The oral *Staphylococcus aureus* in obese and overweight male groups was higher compared to the rate in normal group and these differences were statistically significant (p=0.0261 and p=0.0002 respectively), (Table 1).Among females, the rates of salivary *Staphylococcus aureus* in obese, overweight and normal weight people were 77.8% (28/36), 88.9% (16/18) and 37.5% (12/32) respectively. There were statistically significant differences when comparing the obese (p=0.0007) and overweight (p=0.0004) females with normal weight (control) females (Table 1 and Figure 1).

Generally, the *Staphylococcus aureus* carriage rate in married individuals (68%; 17/25) was higher than the rate in single individuals (60%; 78/130) but this difference was statistically not significant (p=0.452). Regarding the BMI groups, in single people, the oral carriage rates of *Staphylococcus aureus* in obese, overweight and normal weight individuals were 72.1% (31/43), 87.1% (27/31) and 35.7% (20/56) respectively.

In married people, the rates of *Staphylococcus aureus* in obese, overweight and normal weight individuals were 80% (8/10), 80% (8/10) and 20% (1/5) respectively, (Table 2). The rate of oral *Staphylococcus aureus* in obese and overweight single people was significantly higher compared to the rate in the single normal weight people (p=0.0003 and p<0.0001 respectively). In married people, the differences in *Staphylococcus aureus* rates in obese and overweight people com-pared to normal weight people were statistically not significant (p=0.0935)

Figure 1. Male (A) and female (B) distribution of salivary *Staphylococcus aureus* in different BMI groups.

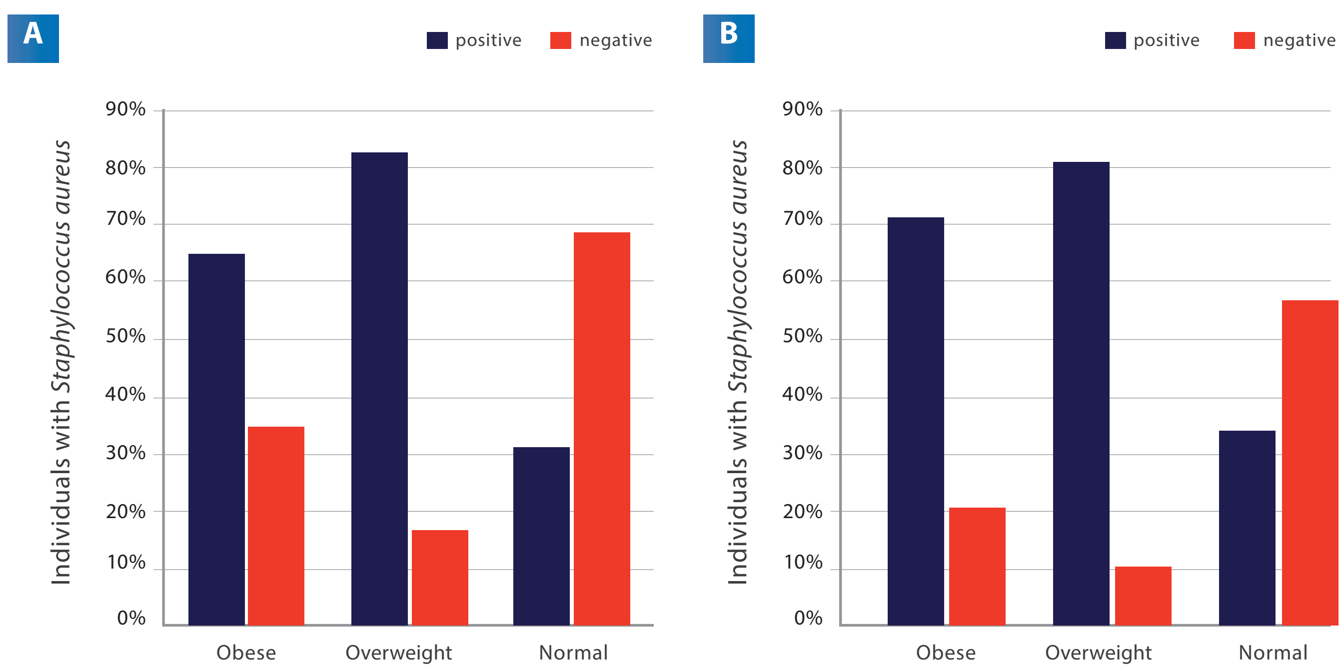

Table 1. Distribution of oral *Staphylococcus aureus* in people with different BMI groups in different genders.

BMI groups (SD)	Gender*	*S. aureus* positive (n=95) (%)	Mean±SD**	*S. aureus* negative (n=60) (%)	Mean±SD**	Total
Obese (n=53)	Male	11 (65)	33.36±2.70	6 (35)	32.93±1.47	17 (25)
	Female	28 (78)	36.96±5.66	8 (22)	33.32±2.53	36 (42)
	Total	39 (73.6)		14(26.4)		53 (34.1)
Overweight (n=41)	Male	19 (83)	27.31±1.33	4 (17)	27.25±0.94	23 (33.3)
	Female	16 (89)	27.45±1.52	2 (11)	28.4±0.98	18 (20)
	Total	35 (85.4)		6 (14.6)		41 (26.4)
Normal weight (n=61)	Male	9 (31)	21.41±1.89	20 (69)	21.76±1.67	29) 42)
	Female	12 (37.5)	20.95±1.99	20(62.5)	21.43±1.54	32 (37.2)
	Total	21 (34.4)		40(65.6)		61 (39.3)

* M: males, F: females. ** Mean weight of individuals, SD=Standard deviation

Table 2. Distribution of salivary *Staphylococcus aureus* in single and married people in different BMI groups.

BMI groups	*Staphylococcus aureus* positive (n=95)		*Staphylococcus aureus* negative (n=60)	
	Single n (%)	Married n (%)	Single n (%)	Married n (%)
Normal (n=61)	20 (35.7)	1 (20)	36 (64.3)	4 (80)
Overweight (n=41)	27 (87.1)	8 (80)	4 (12.9)	2 (20)
Obese (n=53)	31 (72.1)	8 (80)	12 (27.9)	2 (20)
Total	78 (60)	17 (68)	52 (40)	8 (32)

DISCUSSION.

The incidence of obesity has grown significantly. In 2016, globally, overweight and obese adults were about 2 billion and 650 million respectively.[22] During the previous decade, the role of the microbiome in obesity has aroused curiosity, illustrated by several studies on the topic.[5] Obese individuals present predominance of Firmicutes and a relatively low proportion of Bacteroidetes.[23] The oral cavity is colonized by a complex microbiota and the largest and most diverse group is bacteria.[24] Recently, an association between the salivary bacterial profile and obesity was reported in many studies.[7,25,26]

The occurrence of *Staphylococcus aureus*, which belongs to the phylum Firmicutes, as a component of resident oral flora is controversial.[12] The emergence of multidrug resistance in this bacteria is of major public health concern.[27-29] They are generally recognized as transient organisms and relatively few detailed studies of the distribution of staphylococci in the mouth have been conducted.[30]

In the current study, the existence of *Staphylococcus aureus* in saliva samples was studied. The overall carriage of oral *Staphylococcus aureus* was 61.3%. Females had a slightly higher rate (65.1%) than males (56.5%). The rate of carriage in this study was

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higher than in others that reported varied rates of oral S. aureus incidence.[31-33] Also, the current study demonstrated that the frequency of *Staphylococcus aureus* oral carriage was higher in females. This result was in agreement with previous studies showing that *Staphylococcus aureus* oral carriage rate was higher in females than males.[34]

While other studies showed that males were more often carriers than females.[35,36] Although, this insignificant difference of the oral carriage rate of *Staphylococcus aureus* in males and females, the microbial differences between the genders could be due partly to the effects of reproductive hormone modulation of immune defense, microbial virulence, and cell physiology.[37] An increase in weight gain may have a significant impact on human reproductive function in which 6% of female primary infertility is attributable to adiposity.[38]

Although tremendous research focused on the causes of obesity, there is still a misunderstanding of its exact mechanism.[39] In the present study, it was found that the difference of oral *Staphylococcus aureus* carriage rates in obese (73.6%), overweight groups (85.4%) was statistically significant compared to normal weight people (34.4%). These results are in line with other studies: In Baghdad, Iraq, Hamad *et al*.,[20] conducted a study on the correlation of nasal carriage *Staphylococcus aureus* and obesity.

They marked a positive association between high BMI values and nasal carriage of *Staphylococcus aureus*. In another study, a higher occurrence of *Staphylococcus aureus* has been recorded in the saliva of obese women compared with the control group.[21]

However, this study was not in agreement with Stensen *et al*.,[40] who found that the normal weight people were more carriers of throat *Staphylococcus aureus* than overweight and obese people. Our finding suggests that excess body weight could serve as a marker for increased susceptibility to bacterial colonization. Also, this finding may indicate that S. aureus has a role in increasing weight gain in obese and overweight people. The frequency of oral *Staphylococcus aureus* substantially varied between different BMI categories.

A statistically significant difference was observed between the oral abundance of *Staphylococcus aureus* in obese and overweight people in both genders groups compared to normal weight people in these groups. According to previous data, the predictors of *Staphylococcus aureus* are varied by sex and age and some evidence related the status of altered levels of hormones in both sexes such as leptin resistance and sex hormone levels.

Hudek *et al*.,[21] found a higher occurrence of this major human pathogen, *Staphylococcus aureus*, in the saliva of female obese, but a significantly low presence of the bacteria *Streptococcus oralis*, *Streptococcus mitis*, and *Serratia ureilytica* compared with the normal female group. Evidence found a specific species from saliva which belongs to phylum Firmicutes that was related to the overweight status in females. There is strong evidence that the prevalence of Firmicutes, particularly *Selenomonas noxia* can play an important role in the regulation of weight and body composition.[25,26,41]

Although, married people (68%) were insignificantly higher carriers for oral *Staphylococcus aureus* than single people (60%), the *Staphylococcus aureus* rate in single people in the obese and overweight group was significantly higher in comparison to normal weight single people. A previous study, in Taiwan, was in agreement with our results indicating that the nasal carriage rate of *Staphylococcus aureus* was significantly higher in married people compared with unmarried people.[42]

However, another study, in Nigeria, found no significant difference in the colonization rate of *Staphylococcus aureus* in married and single people.[43]

This variation in colonization rate of *Staphylococcus aureus* in married and unmarried people, in a different geographic area, could be due to the fact that the marital status is not a notable factor in colonization and there is no activity or behaviour of any of the groups, which predisposes them to *Staphylococcus aureus* infection.

Interestingly, it was declared that the microbial communities were of greater diversity in married individuals than the unmarried individuals suggesting that human microbiota is influenced by the marital relationships and documenting the health benefits of marriage.[44] Furthermore, it was found that the married individuals have a more similar oral microbiota composition compared to unmarried individuals and this variation of microbial communities can be caused by many factors including the human diet.[45] A high prevalence of *Staphylococcus aureus* nasal colonization has been found among obese people.[17, 18]

Also, a high occurrence of *Staphylococcus aureus* was found to be associated with the saliva of the obese group.[20,21] One possible mechanism by which the microbial species belonging to phylum Firmicutes lead to higher weight and fat gain is their ability for formation SCFA which can provide more calories when they are oxidized by the animal.[46,47] Goodson *et al*.,[25] hypothesized that oral bacteria contribute to obesity by three mechanisms, first, they redirect energy metabolism by increasing insulin resistance in response to increasing tumor necrosis factor (TNF).

Secondly, bacteria increase metabolic efficiency (consuming even small amounts of calories) that causes the body to gain weight without changing the exercise and diet. Third, they can increase the appetite of the host, although there is no research to support this hypothesis.[25]

Furthermore, a strong specific association was found between early intes-tinal colonization with *Staphylococcus aureus* and an increase in circulating soluble CD14, a marker of systemic inflammation. Thus, it was speculated that *Staphylococcus aureus* could act as a trigger of low-grade inflammation, which leads to the development of obesity.[48,49] Also, it was suggested that high levels of serum LPS and chronic exposure to *Staphylococcus aureus* superantigens dysregulates the inflammatory level and triggers body weight gain.[20]

It has been demonstrated that obesity affects the ability of the immune system to adequately respond to an infection caused by some periodontal and dental caries pathogens. Fat is considered as a reservoir for inflammatory cytokines, and it has been suggested that obesity probably affects periodontal disease through this pathway.[50]

Based on data in our study and other similar studies, it is possible to assume that the expansion of some bacteria such as *Staphylococcus aureus* in the saliva may be an indicator of changes in the microbial ecology and contributing to obesity. A potential therapy for controlling the weight gains in both obese and overweight has emerged by selective modulation of gut microbiota using probiotics and/or prebiotics.

This could be an alternative step for classical treatments, including both bariatric surgery and non-surgical multicomponent approaches, which are known to be with side effects and high costs. Obesity is a complex multifactorial condition and the reasons for the connection between obesity and oral bacteria are undoubtedly complex and diverse that relations can be indirect, as they are related to diet, drugs, smoking, or maybe related to different physiological natures of the host.[51,52]

If the human oral microbiome proves to play a key role in pathogenesis and manifestation of obesity, the next step could be new and promising therapeutic approaches such as probiotics or prebiotics, which have already emerged and applied as selective modulation for intestinal microbiota. In the future, oral microbiota will provide a new target for improving the physical state of humans.

Collaborative approaches between obesity and dental professionals need to be further explored to raise awareness and promote better care. Maintaining oral hygiene is necessary to reduce the prevalence of oral opportunistic pathogens. Further studies with larger sample size and individuals with different socioeconomic status may be required to clarify the exact relationship between oral bacteria and obesity

CONCLUSION.

This study provides evidence that salivary *Staphylococcus aureus* was significantly related to the individuals who are clinically labelled obese. The persons with higher BMI are more likely to harbor oral colonization of *Staphylococcus aureus*.

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