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Prevalence of Nasal Carriage S.aureus and methicillin-resistant Staphylococcus aureus (MRSA) among type two diabetes mellitus patients

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Abstract

Staphylococcus aureus (S. aureus) is an opportunistic pathogen that colonizes the anterior nares of about one-third of the human population. Anterior nares colonization with S. aureus or methicillin-resistant S. aureus(MRSA) allows these pathogens to colonize the skin and other anatomical locations. Accordingly, these pathogens may cause different types of endogenous infections. To investigate the prevalence of nasal carriage of S. aureus or MRSA among Iraqi diabetic patients, nasal swabs were taken from 50 diabetic patients, and 50 controls. (52% of the total patients) were found to be colonized with S. aureus, of which 12 (24% of the total patients) were found to be colonized with MRSA. These proportions were higher than those described for the controls population (32% and 18%, respectively) .

Keywords: Staphylococcus aureus Nasal Carriage, MRSA, Type Two Diabetes Mellitus.

مدى انتشار المكورات العنقودية الذهبية والمكورات العنقودية الذهبية المقاومة للميثيسيلين (MRSA) بين مرضى السكري من النوع الثاني

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الخلاصة:

المكورات العنقودية الذهبية هي مسببات الأمراض الانتهازية التي تستعمر فتحتي الأنف الأماميتين لحوالي ثلث السكان. يسمح استعمار الفتحات الأمامية باستخدام المكورات العنقودية الذهبية أو المكورات العنقودية الذهبية المقاومة للميثيسيلين(MRSA) لمسببات الأمراض هذه باستعمار الجلد والمواقع التشريحية الأخرى. وبناء على ذلك، قد تسبب هذه مسببات الأمراض أنواعا مختلفة من الالتهابات الداخلية. للتحقيق في مدى انتشار النقل الأنفي لبكتيريا *S. aureus* أو MRSA بين مرضى السكري العراقيين، تم أخذ مسحات الأنف من 50 مريضا بالسكري، و 50 مجموعة مراقبة. تم العثور على (52٪ من إجمالي المرضى) مستعمرين بواسطة المكورات العنقودية الذهبية، وتم العثور على 12 منهم (24٪ من إجمالي المرضى) مستعمرين بواسطة MRSA وكانت هذه النسب أعلى من تلك الموصوفة لمجموعة السيطرة (32% و 18% على التوالي) .

الكلمات المفتاحية: المكورات العنقودية الذهبية، النقل الأنفي، MRSA، داء السكري من النوع الثاني.

Introduction :

It is commonly acknowledged that diabetes mellitus (DM) poses a serious threat to public health. The phrase "diabetes mellitus" refers to a group of common metabolic and pathological conditions marked by high blood glucose levels. This disorder develops either as a result of the pancreas producing insufficient amounts of insulin or the body's inability to properly use the insulin produced. High blood glucose levels are the hallmark of hyperglycemia, a disease caused by uncontrolled diabetes mellitus. Extended periods of high blood sugar have negative impacts on the body's physiological systems, specifically on blood vessels and neurons. (Al, Haneen and Essam ., 2022; Fayyadh and ALThwani, 2023).

Two primary features of the metabolic disorder known as (T2DM) are diminished insulin production by pancreatic β-cells and decreased responsiveness of insulin-sensitive tissues (Galicia-Garcia *et al*.,2020).

The global incidence of diabetes is experiencing an upward trend,It is prevalence is increasing most rapidly in low- and middle-income countries (Abdul-Hasan and Yassin ,2018). According to Aljulifi (2021), global estimates indicate that over 415 million individuals were affected by diabetes mellitus in 2019. Furthermore, projections suggest that this figure is anticipated to rise to 642 million by the year 2040.In 2017, Iraq recorded a total of 1,411,500 cases of diabetes within its adult population (IDF, 2018).

The pathogenic microbe *Staphylococcus aureus* is in charge of a wide variety of human illnesses that have a major effect on public health.The principal reservoir for S. aureus is the anterior nares, and the development of staphylococcal illness has been linked to the presence of the bacteria in the nasal cavity (Luzzago *et al*., 2014;Al–Shammary *et al*., 2016; Bitrus *et al*., 2018a; Oliveira *et al*., 2018;Cheung *et al*., 2021; Kawada-Matsuo *et al*., 2021;).

Due to its unusual capacity to evade the innate immune response, including mechanisms such as phagocytic, complementary, or antimicrobial peptide (AMP)-mediated death. This unique ability enables the pathogen to survive in various tissues, including the bloodstream. Therefore, *Staphylococcus aureus* is considered to be one of the major microorganisms responsible for causing many diseases. (Kaspar *et al*., 2016; Ansari *et al*., 2019).The virulence of Staphylococcus aureus is attributed to the presence of toxins and enzymes that have the ability to inflict significant harm on tissues and organs. Additionally, these toxins and enzymes are capable of regulating the immune response to these infections (Akrae *et al*.,2021) .

The rise in antibiotic resistance, particularly (MRSA), has caused *S. aureus* to become a major public health concern (Mussa and Al-Mathkhury,2018; Shamkhi *et al*.,2019;Cheung *et al*.,2021; Omar and Mohammed, 2021) .

There is a suggestion that the mechanisms underlying nasal colonization by S. aureus are complex, with the host's immune response being identified as the most significant element (Sakr *et al*., 2018; Ceccarelli *et al.*, 2019).

It is widely acknowledged that those diagnosed with diabetes are often regarded as being more vulnerable to infections, which tend to manifest with greater severity compared to individuals without diabetes(Cockram and Wong,2017;Chávez-Reyes *et al*., 2021).

According to Berbudi *et al*. (2020), the presence of hyperglycemia in individuals with diabetes exerts a significant impact on the immune response to microbial invasion. Previous research has demonstrated that elevated blood glucose levels, known as hyperglycemia, have a detrimental effect on the activation of immune cells' inflammatory genes. Consequently, this impairs their ability to mount an effective inflammatory response against microbial infections (Akbari and Hassan-Zadeh, 2018).

Numerous investigations carried out across many nations have revealed that people with diabetes have a higher incidence of nasal colonization by (MRSA) or *Staphylococcus aureus* than people who are deemed healthy(Tamer *et al.*, 2006;Lin *et al*., 2017; Stacey *et al*., 2019).

Therefore; the aim of this study was to investigate the proportion of nasal colonization with *S. aureus* or MRSA among people in Iraq who were diagnosed with type 2 diabetes **.**

Materials and methods

Sample collection :

Fifty Iraqi patients (females and males) with Type 2 DM (mean age 42.97 ±4.02 years), and and 50 apparently healthy individuals as controls (mean age 46.07 ±3.61 years) whose their gender and age matched the patients group, enrolled in this study . From February 2021 until April 2022, they were enrolled in "The Specialist Center for Diseases of Endocrine and Diabetes" in Baghdad. All patients were selected on the basis of criteria for diabetes which were used according to the American Diabetes Association 2012 guideline (ADA, 2012) ,and were Measurement of Body Mass Index (BMI) patients and controls .

Blood samples collection

Blood samples were obtained from gel tubes and EDTA tubes for the purpose of conducting biochemical investigations. The serum was utilized for the

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quantification of glucose. The evaluation of glucose levels was conducted using the methodology described in reference (Barham and Trinder 1972), with the reagents utilized in the analysis being supplied by Biotek, Spain. The determination of HbA1C is performed using blood taken in an EDTA tube. NycoCard is a Norwegian company.

Bacterial isolation :

Nasal specimens were taken under aseptic conditions from the anterior nares of both patients and controls using sterile nasal swabs. Three clockwise and three counterclockwise rotations were applied to the nasal swab after it was inserted into the nasal cavity at a depth of about one inch.

Immediately after, the swabs were streaked onto blood agar plates and incubated for twenty-four hours at 37°C. Based on their colonial morphology and gram-stained film, the colonies that were thought to be present were subculturing on mannitol salt agar that contained 7.5% sodium chloride. After that, the subcultures were maintained at 37°C for eighteen to twenty-four hours.

Identification of *Staphylococcus aureu*s isolates(Patricia, 2017) :

Bacterial isolates that tested positive for mannitol fermentation, Gram staining, a negative oxidase result, a positive catalase result, and a positive coagulase result were identified as Staphylococcus aureus. The isolates were subsequently verified using the Api staph system

Antibiotic susceptibility tests

Muller-Hinton (MH) agar was used to test the antibiotic susceptibility of Staphylococcus aureus isolates by the disk diffusion (Kirby-Bauer) method. For this study, the antibiotic methicillin (Bioanalyses, Turkey) was used. After measuring the inhibitory zone's diameter, the results were compared to the National Committee for Clinical Laboratory Standard institute's chart (CLSI, 2022).

Results :

Table 1 provides a summary of the clinical characteristics observed in individuals with (T2DM) and a control group of non-diabetic individuals. The average age in the patient's group was found to be 42.97 ± 4.02, whereas in the control group it was 46.07 ± 3.61. There was no statistically significant difference seen among the groups, given the obtained p-value of 0.511.There is no statistically significant disparity in age, as measured by the mean, between the control group and the group with (T2DM).

During the study period, the researchers assessed the body mass index of both patients with T2DM and a group of apparently healthy individuals serving as controls. The findings shown in Table 1 indicate that there is not a statistically significant distinction in body mass index (BMI) between those diagnosed with (T2D) and those who are considered to be in good health. The mean average body mass index (BMI) for individuals with (T2DM) and seemingly healthy controls were found to be 29.5 ± 0.42 and 29.6 ± 0.15, respectively. This indicates that all participants included in the study had a normal body weight.

Serum samples were collected from both patients with (T2DM) and control subjects in order to evaluate fasting blood sugar levels. This study reveals that individuals diagnosed with diabetes exhibit atypical blood glucose levels, namely fasting blood glucose (FBS), in contrast to the control group consisting of healthy individuals. Table (1) shows that a high significant difference was observed in FBS mean level ($p<0.001$) in the patient group (259.67 ± 12.72) and in the control (89.00 ± 1.72).

The HbA1c levels were assessed in specimens obtained from both patients diagnosed with (T2DM) and individuals considered to be in good health as controls. The findings presented in Table 1 indicate a statistically significant rise ($P>0.0001$) in the mean average of glycated hemoglobin levels. Specifically, the mean average increased from (4.49 ± 0.44) in the blood specimens of the seemingly healthy control group to (8.08 ± 0.91) in the serum specimens of the group consisting of patients with (T2DM).

Table 1. presents a statistical study comparing the variables of Age, BMI, FBS, and HbA1c between patients and healthy controls.

Parameter	$Patient\ (n = 50)$	$Control\ (n = 50)$	$t-test$ $P-Value$
Age (year)	42.97 ±4.02	46.07 ±3.61	0.511 NS
BMI (Kg/m2)	29.5 ± 0.42	29.6 ± 0.15	0.4108NS
FBS (mg/dl)	259.67 ± 12.72	89.00 ± 1.72	0.0001**
HbA1c (%)	9.09 ±0.20	5.23 ± 0.08	0.0001**
NS:NonSignificant ** ($P\leq0.01$)			

Data are shown as mean ± SD. FBS: Fasting blood sugar, HbA1c: Hemoglobin A1c, BMI: Body mass index, SD: Standard deviation

As previously stated, the primary objective of this study was to ascertain the prevalence of nasal colonization with Staphylococcus aureus or (MRSA) among individuals in Iraq diagnosed with Type 2 diabetes. In order to accomplish this goal, an initial step was taken to gather nasal swabs from a sample of 50 patients diagnosed with type II diabetes (as shown in Table 1). Additionally, a control group consisting of 50 persons who are in good health was included in the study.Based on the findings obtained using traditional methods such as culture, biochemical analysis, and the API Staph system, it was observed that nasal colonization of Staphylococcus aureus (NCSA) was prevalent in 52% of patients with (T2DM) compared to a prevalence of 32% in the control group.

Table (2): Nasal carriage % of S. aureus in patients with type 2 diabetes compared to controls.

Nasal Carriage of S. aureus	T2DM Patients groups		Healthy control groups	
	No.	%	No.	%
Number	26	52	16	32
Total Number	50	-	50	-

(MRSA) was detected in the acquired isolates through the assessment of susceptibility to methicillin (5 µg), following the guidelines set forth by the Clinical and Laboratory Standards Institute (CLSI) in 2022. Out of the 26 isolates of S. aureus that were recovered, 12 (representing 24% of the total patients) and 9 (representing 18% of the total controls) were identified as MRSA isolates, as shown in Table 3.

Table (3): MRSA and MSSA nasal carriage rate among T2DM Patients and Healthy controls .

S. aureus	*Patients groups*		*Healthy control gro*	
	No.	%	*No.*	%
MRSA	12	24	9	18
MSSA	14	28	7	14

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Discussion :

Several investigations have indicated that there is no statistically significant disparity in the prevalence of nasal colonization by S. aureus between diabetic patients and persons who are considered healthy. According to a number of research (Essigmann *et al*., 2022), it has been observed that diabetes mellitus serves as a risk factor that enhances the probability of S. aureus colonization in the anterior nares (Lin *et al*., 2017;Stacey *et al*., 2019). T2DM is distinguished by the dysregulation of the innate immune system, resulting in a heightened occurrence of nasal Staphylococcus aureus colonization. This colonization serves as a significant risk factor for the development of severe infections.(*Sakr et al*., 2018; Plataki *et al*., 2021;). Furthermore, increased levels of glycated hemoglobin (HbA1c) in diabetic patients have been shown to significantly increase the rate of colonization of the anterior nares by S. aureus, and oral hypoglycemic medications reduce this rate. Improved management of diabetes mellitus has the potential to mitigate the development of Staphylococcus aureus colonization and thus decrease the susceptibility to subsequent infections (Lin *et al*., 2020).

Additionally, a separate investigation revealed that the prevalence of nasal carriage of Staphylococcus aureus (NCSA) among individuals in Iraq diagnosed with (T2DM) was 56.10%, whereas the control groups exhibited a prevalence of 36.58% (Hamad *et al*., 2018). According to ALKazaz, (2014), the prevalence of Staphylococcus aureus in nasal samples was shown to be 40%. Additionally, a separate study revealed a higher incidence of nasal carriage of Staphylococcus aureus (NCSA) in individuals with diabetes compared to the control group. This finding aligns with the research conducted by Ahluwalia *et al*. (2010), which reported a prevalence of 56.6% for NCSA in diabetic patients, whereas the control group exhibited a prevalence of 14.8%.

Individuals diagnosed with diabetes had a significantly greater likelihood of becoming carriers of S. aureus (31.0% vs. 10.4%), although no significant difference was observed in the prevalence of MRSA (3.3% vs. 0.0%). It is noteworthy to acknowledge that previous instances have demonstrated a correlation between a certain group at risk and an increased likelihood of S. aureus carriage, albeit not necessarily MRSA carriage (Donkor *et al*.2019; Appiah *et al*.2020;Anafo *et al*.,2021) .

Using a meta-analysis, researchers from a variety of countries and areas, such as East Asia, the Middle East, Germany, Taiwan, and the United States, looked into the prevalence of S. aureus and MRSA colonization of the anterior nares among diabetes patients. Colonization rates for MRSA were 8.33% and for S. aureus they were 13.46%, according to the study (Stacey *et al*., 2019). However, we found that the percentage of MRSA and *S. aureus* colonizing the nose was lower than the percentage we observed in our investigation.

According to the current study's findings, around 52% of diabetic persons had S. aureus colonization, while approximately 24% had MRSA colonization. In comparison to the proportions reported in a study carried out in Palestine in 2023, the observed proportions of nasal colonization with S. aureus and MRSA in the current inquiry were found to be larger (Abbas *et al.*, 2023). As per the cited study, around 35.1% of the patients had S. aureus colonization, while 9.7% had MRSA colonization.

A study conducted in Iran on diabetic patients reported that nasal colonization of Staphylococcus aureus and MRSA was 42.5%, 24.6% respectively (Alizargar *et al*.,2013), In this study, nasal carriage rate of S.aureus which is lower than our study but colonization of MRSA nasal carriage was higher than our study .

A study by Rani *et al*. (2015) among diabetes patients in India revealed a significant frequency of (MRSA) isolates (18.42%) and Staphylococcus aureus (63.3%). In contrast, the prevalence of nasal carriage of S. aureus in the present study was found to be higher compared to our previous study. However, the colonization rate of MRSA in the nasal carriage was to be lower in this study as compared to our investigation.The observed discrepancy could perhaps be attributed to variations in the sample size and the methodology employed for detection.

People in Saudi Arabia who have been diagnosed with type 2 diabetes participated in a study. According to a study by Lin *et al*. (2017), 72.41% of hemodialysis patients (HD) had nasal carriage of S. aureus, and 18.97% of these people also carried MRSA.

A comparable investigation conducted in Australia by Hart J. revealed that among diabetic patients, 39.1% tested positive for S. aureus, while 3.1% were found to be carriers of MRSA. The findings of this study indicate a lower value than our study. The observed discrepancy could potentially be attributed to variations in sample size, research group composition, and differences in the procedure employed for obtaining swab samples (Hart *et al*., 2015).

Based on the aforementioned figures, it is evident that the occurrence of S. aureus nasal carriage among individuals with diabetes varies throughout countries and locations. Moreover, there is a higher likelihood for individuals with diabetes to carry S. aureus.

The observed discrepancies in the nasal carriage rate of S. aureus across various studies may be attributed to variations in the characteristics of the study population, sampling methods, culturing techniques, geographical distribution, and diagnostic approaches (Tigabu *et al*., 2018).

The presence of this microorganism can be attributed to its role as a significant contributor to both hospital-acquired (nosocomial infections) infections and infections acquired within the community, which can have severe consequences (Diekema *et al*., 2001; Crossley *et al*., 2009). It is considered an important pathogen capable of causing opportunistic infections due to its membership in the normal flora of the human body (Tong *et al*., 2015). Furthermore, it possesses numerous virulence factors that facilitate tissue penetration and contribute to the development of infection (Zadik *et al*., 2001).

Nevertheless, *Staphylococcus aureus* is classified as an opportunistic pathogen capable of being isolated from several sources of infection and inducing infections in humans. There has been a notable increase in community-acquired infections caused by *Staphylococcus aureus*. Significant clinical symptoms of infections caused by *S. aureus* include pleuropulmonary infections, skin and soft tissue infections, bacteremia, and infective endocarditis. Meningitis, urinary tract infections, spinal abscesses, and toxic shock syndrome are further clinical infections (Tong *et al*., 2015; Park *et al*.,2021).

Conclusion :

The participants who had diabetes were shown to have a nearly two folds increased likelihood of being carriers of S. aureus, but not MRSA. In addition, surveillance studies on (MRSA) among diabetes patients and other risk populations must be maintained of S. aureus and MRSA colonization. One of the disadvantages of this study was the relatively limited number of enrolled participants.

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Iraqi Journal of Humanitarian, Social and Scientific Research
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