

Original Article

Staphylococcus aureus Nasal Carriage and Associated Factors in Type 2 Diabetic Patients

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SUMMARY: We aimed to compare the rate of nasal carriage of *Staphylococcus aureus* (NCSA) between type 2 diabetic patients and non-diabetic ones and also to reveal the associated risk factors. Type 2 diabetic subjects were selected from outpatient diabetes clinics and control subjects were selected from outpatient internal medicine clinics in the same hospital. The subjects were divided into 3 groups. Group I included 68 subjects on insulin therapy and dietetic treatment, Group II included 80 subjects on oral anti-diabetic agents and dietetic treatment and Group III included 150 age- and sex-matched non-diabetic subjects. The rates of NCSA for Group I, II and III subjects were found to be 24 (35.3%), 11 (13.8%), and 16 (10.7%), respectively. Whereas there was no significant difference in NCSA positivity between Group II and Group III, a significant difference was found between Groups I and III ($P < 0.01$). Univariate analysis revealed that the following were significant risk factors for NCSA in our diabetic patients: insulin use, hospital admission within the last 6 months, being diabetic for more than 6 years, fasting glucose level above 111 mg/dl and antibiotic usage within the last 6 months. Furthermore, insulin use (odds ratio 3.32) and antibiotic usage within the last 6 months (odds ratio 5.75) were defined as significant risk factors for NCSA in diabetic subjects by the logistic regression method. Our results suggested that the rate of NCSA was significantly higher in type 2 diabetic patients who used insulin or antibiotics within the last 6 months.

INTRODUCTION

Staphylococcus aureus is a major human pathogen that causes a variety of infections in both healthy and immunocompromised individuals. The infections associated with *S. aureus* can lead to numerous complications, and in some cases can result in death (1,2). Nasal carriage of *S. aureus* (NCSA) plays a key role in staphylococcal infections (3). Longitudinal studies have found that 10 to 35% of healthy adults persistently carry *S. aureus* in their nares, that 20 to 75% of healthy adults are intermittent carriers, and that 5 to 70% of healthy adults do not carry the organism (4). The incidence of *S. aureus* nasal carriage may increase under various conditions, such as in patients after surgery, patients receiving continuous ambulatory peritoneal dialysis, and patients receiving hemodialysis (3). Several studies have shown that elimination of carriage in the anterior nares, the principal reservoirs of *S. aureus*, reduces the incidence of *S. aureus* infections (5).

Diabetics show a high rate of *S. aureus* associated infections (6-8), and thus NCSA in diabetic patients should be a considerably important research topic. Unfortunately, however, there have been only a few studies on the rate of NCSA in diabetic patients (10-17), and these studies have tended to have limitations, such as a limited number of subjects (11-15), the indiscriminate inclusion of both type 1 and type 2 diabetics (12,16), or the inclusion of only pediatric-age groups (17). Nonetheless, with the exception of a study

with conflicting results (9), these works have generally found higher rates of NCSA in diabetic patients than in the general community.

Is the rate of NCSA truly higher in adult type 2 diabetic patients? What are the factors affecting NCSA in diabetic patients? These questions have not been clearly answered. In this study, therefore, we compared the rates of NCSA between adult type 2 diabetic patients and non-diabetic patients, and investigated possible risk factors associated with NCSA.

MATERIALS AND METHODS

Subjects: This study was carried out at the Izzet Baysal School of Medicine between March 2003 and December 2004. Diabetic subjects were selected from among patients who were being observed for at least 6 months at the Izzet Baysal Faculty of Medicine outpatient diabetes clinics. Diabetic subjects were observed by our diabetes clinics once each month.

The subjects were divided into three groups as follows: Group I included 68 subjects on insulin therapy and dietetic treatment (28 males [M] and 40 females [F]; average age, 61.0 years; range, 42 - 80 years). Group II included 80 subjects on oral anti-diabetic agents (OAD) and dietetic treatment (35 M and 45 F; average age, 63.4 years; range, 41 - 83 years). Group III included 150 age- and sex-matched non-diabetic patients (59 M and 91 F; average age, 61.2 years; range, 42 - 82 years). All subjects completed a standard form including information on their past diseases, drug usage and allergy history, and all subjects provided written informed consent to participate in the study.

Diagnosis of diabetes: Diagnosis of diabetes was based on the criteria defined by Kuzuya et al. (18). In brief, (i) fasting glucose level (FPG) ≥ 126 mg/dL; (ii) plasma glucose

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level ≥ 200 mg/dL after giving 75 g glucose (2hPG); (iii) glucose level ≥ 200 mg/dL measured at any time; (iv) diabetes diagnosed after the age of 30; (v) insulin not required within the first 6 months of diagnosis. Patients using OAD or insulin or one or more of the above criteria were diagnosed as diabetic. Insulin and oral anti-diabetic agents to be used by the patients were determined according to glucose level.

Subjects in the control group were selected from among outpatients who consulted the outpatient internal medicine clinics of the same hospital and who were confirmed not to have diabetes (FPG below 110 mg/dl and 2 hPG below 140 mg/dl) (18).

Exclusion criteria: HIV positive patients, cirrhotic patients, patients on anti-staphylococcal drug treatment that were started within the last 10 days for any reason, patients on immunosuppressive treatment, patients having pyogenic skin infection within the last 1 month and patients having chronic renal failure were excluded from the study.

Nasal specimens and microbiologic procedures: Nasal specimens were collected for each subject using two sterile cotton-wool swabs. Swabs were rotated three times clockwise and three times anticlockwise in the anterior nares of the nose (19). At least two nasal specimens were obtained from the subjects, because nasal carriage is defined as at least two consecutive *S. aureus* isolates from the anterior nares in a 5-day period. The microbiologist who examined the culture plates and reported the microbiological results was blinded to the subject groups. The swabs were immediately placed in Stuart's transport medium and kept at 4°C before being inoculated onto mannitol salt agar (Chapman Medium; BioMérieux, Marcy l'Etoile, France). The plates were incubated at 37°C for 48 h. All mannitol-positive colonies were subcultured onto 5% blood agar, and *S. aureus* isolates were defined as catalase-producing Gram-positive cocci that were positive for tube coagulase and confirmed by a rapid *S. aureus*-specific latex agglutination test (Staphaurex Plus; BioMérieux). Cases in whom nasal cultures were more than three colonies yielded for *S. aureus* were considered carriers (20).

Statistical analysis: All variables were expressed as the mean values \pm SD, range or number of patients and percentages. A logistic regression model was used to determine which factors could predict NCSA and to control the effects of potential confounding factors. In the initial logistic model,

all variables associated with the dependent variable in univariate analysis (χ^2 or Fisher's exact tests) were included, with values of $P < 0.20$ considered to indicate statistical significance. In this model, the dependent variable was NCSA (dichotomous variable). The independent variables were age, sex, diabetic treatment (insulin group or OAD), antibiotic usage within the last 6 months, hospital admission within the last 6 months, dermatitis, liver diseases, duration of diabetes and fasting glucose level. Variables with statistically significant associations ($P < 0.05$) with NCSA were kept in the final model. Also, some characteristics of the patients in the diabetic treatment groups were compared by ANOVA. Analyses were performed using SPSS software (Version 9.05 for Windows; SPSS Inc., Chicago, Ill., USA).

RESULTS

A total 298 subjects were enrolled in the present study. Comparisons of the characteristics of NCSA-positive and -negative subjects are presented in Table 1.

When NCSA-positive and -negative subjects were compared by univariate analysis, no statistically significant difference was found between the groups regarding factors such as age, sex, dermatitis and liver diseases except for cirrhosis. Univariate analysis revealed that the following were significant risk factors for NCSA in our diabetic patients: insulin use, hospital admission within the last 6 months, being diabetic for more than 6 years, fasting glucose level of above 111 mg/dl and antibiotic usage within the last 6 months. Furthermore, insulin use (odds ratio [OR] 3.32) and antibiotic usage within the last 6 months (OR 5.75) were defined as significant risk factors for NCSA in diabetic subjects by the logistic regression method (Table 2).

There were no significant differences in gender or mean age among Groups I, II and III ($P > 0.05$). Among all subjects, the rate of NCSA was 51/298 (17.1%). The rates of NCSA in Groups I, II and III were 24 (35.3%), 11 (13.8%), and 16 (10.7%), respectively. Whereas there was no significant difference between Groups II and III regarding NCSA positivity, a significant difference was found between Groups I and III ($P < 0.01$). The clinical characteristics and comparisons of the Groups are presented in Table 3.

Table 1. Comparisons of nasal carriage of *Staphylococcus aureus* (NCSA) positive and negative subjects

Characteristics	NCSA (-) n (%)	NCSA (+) n (%)	P value
Number	247 (82.9)	51 (17.1)	
Males:Females	99 (41.1): 148 (59.9)	23 (45.1): 28 (54.9)	0.507 ¹⁾
Age [years]	61.6 \pm 9.2 [42-83]	62.4 \pm 10.1 [43-80]	0.606 ²⁾
Diabetic patients on insulin therapy	44 (17.8)	24 (47.1)	0.0001 ¹⁾
Dermatitis	7 (2.8)	1 (2.0)	1.000 ³⁾ (0.835 ¹⁾)
Hospital admission within the last 6 months	14 (5.7)	13 (25.5)	0.0001 ³⁾ (0.000 ¹⁾)
Antibiotic usage within the last 6 months	14 (5.7)	17 (33.3)	0.0001 ¹⁾
Liver diseases	11 (4.5)	3 (5.9)	0.714 ³⁾
Having diabetes for over 6 years	53 (21.5)	24 (47.1)	0.0001 ¹⁾
Having fasting glucose level of ≥ 111 mg/dl	107 (43.3)	34 (66.7)	0.002 ¹⁾

¹⁾: χ^2 test was used.

²⁾: T-test was used.

³⁾: Fischer's exact test was used.

Table 2. Logistic regression results of significant variables by univariate analysis

Variables	Odds Ratio	95% Confidence interval	P value
Diabetes state			
Non-diabetic	1		
Not using insulin	0.99	0.35-2.78	0.991
Using insulin	3.32	1.39-7.91	0.006
Antibiotic usage within the last 6 months			
No	1		
Yes	5.75	2.12-15.59	0.0001
Hospital admission within the last 6 months			
No	1		
Yes	2.24	0.73-6.87	0.155

Table 3. Clinical characteristics and comparison of the Groups

Characteristics	Group I (Type II diabetic on insulin therapy) n = 68	Group II (Type II diabetic on OAD therapy) n = 80	Group III (Non-diabetic group) n = 150
Age (years)	61 ± 9.3 (42-80)	63.4 ± 9.2 (41-83)	61.2 ± 9.3 (42-82)
Male/Female	28/40	35/45	59/91
Mean fasting glucose level mg/dl (range)	135.4 ± 21.2 (70-200)	139.6 ± 15.3 (120-183)	86.7 ± 10.7 (64-105)
Skin diseases	2	2	4
Liver diseases	7	4	3
Hospital admission within the last 6 months	11 ¹⁾	8 ²⁾	8 ³⁾
Antibiotic usage within the last 6 months	12 ⁴⁾	9 ⁵⁾	10 ⁶⁾
NCSA positivity	24	11	16

OAD, oral anti-diabetic agents; NCSA, nasal carriage of *Staphylococcus aureus*.

Eleven patients were hospitalized in Group I¹⁾, 6 of them had diabetic regulation, 1 had a retina operation, 1 had a cataract operation, 2 had hypertension and 1 had lower respiratory system infection; in Group II²⁾, 4 had diabetic regulation, 2 had hypertension and 2 had chronic obstructive lung disease; and in Group III³⁾, 3 had lower respiratory system infection, 1 had urinary system infection, 2 had hypertension, 1 had angiography and 1 had psoriasis. Twelve patients used antibiotics in Group I⁴⁾, 7 of them took quinolones and trimethoprim-sulfamethoxazole due to urinary system infection, 3 took quinolones due to lower respiratory system infection, and 2 took β -lactam antibiotics due to upper respiratory tract infection; in Group II⁵⁾, 6 took β -lactam antibiotics and macrolides due to upper respiratory tract infection, 1 took quinolones due to urinary system infection and 2 took β -lactam antibiotics due to lower respiratory system infection; in Group III⁶⁾, 3 took β -lactam antibiotics due to lower respiratory system infection, 2 took quinolones due to urinary system infection, 3 took quinolones due to gastroenteritis and 2 took β -lactam antibiotics due to upper respiratory system infection.

DISCUSSION

Infections associated with *S. aureus* are frequently observed in diabetic patients and lead to significant morbidity and mortality (21). NCSA is a significant risk factor for staphylococcal infections (1,3). In the present study, the rate of NCSA in Group II subjects was not different from that in the control group (95% CI 0.35-2.78; $P > 0.05$). However, in the few studies carried out to date, it has been reported that the rate of NCSA in diabetic patients is higher than that in the general population. The data from these studies are summarized in Table 4. This disparity between our study and the past studies may have been related to one or more of the following factors. (i) Our study included a larger number of subjects than the previous studies. (ii) In most of the past studies, diabetic subjects were not grouped according to the treatment methods. However, we divided our type 2 diabetic patients according to treatment methods in this study. (iii) Whereas only univariate analysis was used in the past studies, in this study we also used multivariate logistic regression analysis. (iv) Whereas some of the past studies included both type 1 and type 2 diabetic patients, our study included only type 2 diabetic patients. (v) Whereas some of the past studies included both adults and pediatric-age groups, our study included only adults. It is well known that persistent carriage

is more common in children than in adults, and the frequency of carriage decreases in individuals over 10 years of age (22,23). (vi) The criteria used to assign an individual to either carriage pattern have varied from study to study in terms of both the interval and the number of cultures performed and the required proportion of cultures that grow *S. aureus*. Today, persistent nasal carriage is considered to exist in individuals for whom serial nasal swab specimen cultures consistently yield *S. aureus* (24). In our study nasal carriage was defined as the detection of at least two consecutive *S. aureus* isolates from the anterior nares in a 5-day period. However, in the past studies NCSA was defined based on only a single nasal culture. This situation may be another cause for disparity.

Our univariate analysis revealed that hospital admission within the last 6 months, having diabetes for over 6 years, and a fasting glucose level of 111 mg/dl or above were significant risk factors for NCSA. These conditions were also described as risk factors for NCSA in the past (25,26). Cases using insulin, frequent admission, long history of diabetic status, high fasting glucose level are all confounding each other and have interactions between them. But these variables were not found as significant in the logistic regression model.

In our study, the rate of NCSA in type 2 diabetic subjects

Table 4. NCSA positivity rates from the reported studies¹⁾

Reference (no.)	Diabetics (n)	Carriage rate (%)	Control (n)	Carriage rate (%)
Ahluwalia et al. (12)	Type 1 diabetics (31)	67.7	Control (27)	14.8
	Type 2 diabetics (29)	44.8		
Berman et al. (11)	Type 1 diabetics (71)	46.5	Medical students (116)	50.5
Boyko et al. (10)	Type 2 diabetics (188)	27.0	Control (363)	14.8
Chandler and Chandler (16)	Diabetics (30)	35.0	Control (30)	11.0
Lipsky et al. (15)	Type 2 diabetics (59)	30.5	Control (44)	11.4
Smith and O'Connor (17)	Diabetic children (157)	76.4	Children (374)	44.3
Singh and Rao (13)	Diabetics (33)	21.2	Control (33)	27.2
Tuazon et al. (14)	Diabetics on insulin (30)	34.0	Control (15)	11.0
	Diabetics on OAD (36)	11.0		
This study	Type 2 diabetics on insulin (68)	35.3	Control (150)	10.7
	Type 2 diabetics on OAD (150)	13.8		

¹⁾: Adapted from reference 12.
OAD, oral anti-diabetic agents.

who use insulin was found to be considerably higher than that in the control group. Other investigators have also reported this finding (12,14). The question of why patients using insulin should have a higher rate of NCSA than non-insulin-using diabetics has not been adequately addressed. However, NCSA has frequently been reported in patients who are exposed to repetitive injection (such as hemodialysis patients and IV drug abusers) (27,28). Similarly, we thought that the higher NCSA rate in the insulin-using group in the present study might have been related to skin damage due to repetitive needle puncture. Intact skin is by nature an excellent barrier to infection. The heightened risk of infection in the puncture wounds of diabetic patient calls into question the common practice of syringe reuse in impoverished nations. Touching the needle to the skin may also transfer ubiquitous skin organisms to the needle. If the contaminated syringe is discarded after a single use, the risk of infection is minimized. However, if the moistened, contaminated syringe is reused, there may be ample time for organisms to multiply (via binary multiplication) to high levels (29; available online at <http://www.uspharmacist.com/oldformat.asp?url=newlook/files/cons/cyp11.htm>). In many developing nations, including Turkey, insulin injections have sometimes been made repeatedly with the same needle due to financial restraints.

The rate of NCSA was significantly higher in patients who had used antibiotics within the last 6 months. Previous studies have also suggested an association between antibiotic usage and NCSA (30,31). Whereas susceptible microorganisms in the normal flora decrease due to the antibiotic usage, resistant microorganisms increase (3). For example, in patients who are given penicillin and tetracycline, *S. aureus* resistant to these drugs colonize in the nasal mucosa, and then these patients spread the resistant microbe to other people (32). The most commonly prescribed antibiotics in our subjects were fluoroquinolones and β -lactams. Both drugs can be easily excreted by sweat and secretions and can reach to concentrations that exceed minimum inhibitory concentrations in cutis (33). Therefore the normal bacterial flora in cutis is suppressed, and consequently bacteria resistant to these drugs colonize in such places (34,35).

In the present study, we found that the rate of NCSA in diabetic patients who did not use insulin was not different from that in the controls. On the other hand, the rate of NCSA was significantly higher in type 2 diabetic patients who used insulin or who had used antibiotics within the last 6 months. Based on these results, we conclude that type 2 diabetes does

not affect NCSA, but using insulin increases the risk for NCSA in type 2 diabetic patients.

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