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ASSOCIATION BETWEEN METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* INFECTION AND VITAMIN D DEFICIENCY

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ABSTRACT

ASSOCIATION BETWEEN METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* INFECTION AND VITAMIN D DEFICIENCY

By Jenna L. Thomason

Purpose. Given that vitamin D (25(OH)D) contributes to immunity, we sought to determine if 25(OH)D deficiency was significantly associated with Methicillin-resistant *Staphylococcus aureus* (MRSA) infection. ***Methods.*** All patients with 25(OH)D determinations at the Atlanta VAMC from 2007-10 were included in the analyses. The first recorded 25(OH)D level was used for each patient. These patients were matched with an on-going study of patients with well-characterized MRSA infection (2005-10) and were considered cases; patients with 25(OH)D determinations without an MRSA infection were controls. Multivariate logistic regression was used to determine the independent association between 25(OH)D level, dichotomized into deficient (<20 ng/mL) vs. non-deficient (≥20 ng/mL), and case/control status. ***Results.*** A total of 6405 patients with 25(OH)D determinations were included in the analyses, of which 401 (6.3%) experienced an MRSA infection during the study period. The majority of the MRSA infections were skin and soft tissue infections (SSTIs) (n=232; 57.9%) and almost all were diagnosed in the outpatient setting (n=366; 91.3%). Mean (*SD*) vitamin D levels were 21.1 (*12.4*) and 24.0 (*12.6*) for cases and controls, respectively ($p<0.0001$). MRSA infection was also significantly associated with younger age ($p=0.0008$), male gender ($p=0.0023$), lower BMI ($p<0.0001$), and HIV positive status ($p<0.0001$) in the univariate analyses. The multivariate logistic regression model confirmed an independent association for gender, race, BMI, HIV status, and 25(OH)D (OR for 25(OH)D: 1.63; 95% CI: 1.31-2.03). Sensitivity analyses using only SSTIs or outpatient cases still revealed 25(OH)D as an independent risk factor, although in the former model the association was not significant. ***Conclusions.*** MRSA cases had significantly lower serum 25(OH)D levels than controls, even when controlling for age, gender, BMI, HIV status, and race. Further study is necessary to investigate this association in other populations and to determine if optimization of 25(OH)D levels could potentially be useful for prevention or treatment of MRSA infection.

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BACKGROUND

Vitamin D is best known for its role in bone metabolism; however, in recent years, deficiency of this fat-soluble vitamin has gained attention for its role in number of other pathologic processes, including musculoskeletal diseases, cardiovascular disease, certain types of cancer, autoimmune diseases, psychiatric illnesses, lung function,[1] diabetes mellitus,[1,2,3] renal disease,[4] and infection.[5] In addition, a recent meta-analysis showed that supplementation with vitamin D is associated with decreased all-cause mortality.[6]

Several forms of vitamin D exist. Vitamins D_2 and D_3 can be obtained from either natural food sources including oily fish, shitake mushrooms, egg yolks, or fortified food sources such as milk, orange juice, cereal, and over-the-counter supplementations. Vitamin D_2 is also available by prescription for supplementation and vitamin D_3 is the form of the vitamin produced in the skin from 7-dehydrocholesterol after exposure to ultraviolet B (UVB) light. Following synthesis in the skin, vitamin D_3 is hydroxylated in the liver to 25-hydroxyvitamin D (25(OH)D); this is the form used to determine a patients' vitamin D status. The active vitamin D hormone, 1,25 hydroxyvitamin D ($1,25(OH)_2D$), is then created in the kidney after 25(OH)D undergoes hydroxylation by the 1α-hydroxylase enzyme (CYP27B1). When circulating 25(OH)D is available, the active hormone can also be produced locally in cells that that contain the 1α-hydroxylase enzyme.[1,5] Deficiency may result from a number of causes, including reduced synthesis in the skin, decreased bioavailability, increased catabolism, decreased synthesis of 25(OH)D or $1,25(OH)_2D$, or increased urinary loss of 25(OH)D.

Reduced synthesis in the skin may occur due to sunscreen use or sun avoidance, absorption of UVB radiation by melanin in darker skinned individuals, or reduced 7-dehydrocholesterol in the skin of elderly individuals or patients with skin grafts for burns. Synthesis of vitamin D also varies by potency of the sunlight, and therefore varies by season, latitude, and time of day when individuals are exposed. Decreased bioavailability of vitamin D may occur in the setting of obesity or due to malabsorption of fat caused by diseases or medications. Medications may also cause increased catabolism of vitamin D. Decreased synthesis of 25(OH)D occurs in the setting of liver dysfunction or failure and increased excretion of 25(OH)D may result from nephrotic syndrome. Chronic kidney disease may lead to decreased synthesis of $1,25(OH)_2D$.[1] Breast milk has low vitamin D content; therefore infants who receive breast milk as their sole source of nutrition are at risk for vitamin D deficiency.[1]

There is currently no consensus on optimal serum vitamin D level. In the past, vitamin D deficiency and vitamin D insufficiency were defined according to variations in parathyroid and intestinal calcium transport as serum 25(OH)D < 20 ng/mL and serum 25(OH)D 20 - 29 ng/mL, respectively.[1] More recently, the Institute of Medicine conducted a review of all of the data available on vitamin D and found that the benefit of this vitamin for the majority of the population is achieved with a serum 25(OH)D level of approximately 20 ng/mL.[7] The authors remarked, however, that many uncertainties continue to surround vitamin D since its physiology and metabolism are incompletely understood, there continues to be variability in measures of serum 25(OH) vitamin D owing to different

methodologies used, and the cut points defined for deficiency of vitamin D have yet to undergo a thorough, systematic investigation.[7]

However, all of the proposed definitions for deficiency label many people in the United States as vitamin D deficient. According to the most recent data available from the National Health and Nutrition Examination Surveys (NHANES), 32% of the US population aged 1 year and over had serum 25(OH)D levels <20 ng/mL.[8] Even with the increasing attention on vitamin D in recent years, serum levels in the US population have declined. NHANES III (1988-1994) revealed a mean serum 25(OH)D level of 30 (95% CI: 29-30) ng/mL; this number decreased to 24 (95% CI: 23-25) during NHANES 2001-2004. The decrease is hypothesized to stem from increasing sun protective behaviors to prevent skin cancer and premature aging, as well as the shift to indoor activity.[9]

Numerous studies have identified non-Hispanic black persons and Mexican Americans as having higher rates of deficiency than white individuals.[8,10] In general, males, children, and lean individuals have been found to have higher vitamin D concentrations than their counterparts.[8,10] The inverse relationship between BMI and vitamin D is clearer in non-Hispanic white women than non-Hispanic black women.[10]

Individuals with inadequate vitamin D status may have a higher risk of certain infections. In fact, it has been shown that serum vitamin D levels enhance immune function in a dose-dependent manner.[11] To date, vitamin D has been found to contribute to barrier integrity as well as both the innate and adaptive immune systems.[5]

The body's first line of defense, or barrier, against invasion of pathogens is formed by the epithelial cells of the skin, gastrointestinal, respiratory, and urinary tracts. These epithelial cells are connected by cell junctions, including tight junctions (e.g. occludin), gap junctions (e.g connexion 43), and adherens junctions (e.g. E-cadherin), all of which require proteins encoded by genes which are upregulated by $1,25(OH)_2D$ via the 1α-hydroxylase enzyme.[5]

Vitamin D contributes to innate immunity by stimulating the production of antimicrobial peptides, including one defensin (hBD-2) and cathelicidin (LL-37) in response to injury, inflammation, or infection. The production of these two peptides is dependent on an adequate supply of circulating 25(OH)D.[5] HBD-2 is produced by epithelial cells of the skin (keratinocytes), and gastrointestinal, genitourinary, and lower respiratory tracts, and has antimicrobial activity mainly against gram negative bacteria. Additionally, hBD-2 mediates chemotaxis of T-cells, and facilitates chemotaxis, maturation, and activation of dendritic cells. Therefore, hBD-2 provides a connection between the innate and adaptive immune systems.[12] Cathelicidin has been identified in epithelial cells, sweat glands, saliva, neutrophils, monocytes and other tissues and has broad spectrum antimicrobial activity against both gram positive and gram negative bacteria.[12,13] This peptide also has the ability to bind lipopolysaccharide and neutralize its endotoxin activity.[13] Furthermore, cathelicidin increases vascular permability, promotes wound healing and cell proliferation, binds and acts as a chemotactic factor for neutrophils, monocytes, T cells, and mast cells.[5,13] Vitamin D also contributes to the killing of certain fungi and bacteria by oxidative burst, which is

the rapid release of reactive oxygen species in monocytes and neutrophils.[14] Specifically, active vitamin D incites hydrogen peroxide secretion in monocytes, resulting in increased oxidative burst potential.[15]

Over reaction of the inflammatory response of the innate and adaptive immune systems can lead to cell and tissue damage. Vitamin D may prevent over reaction by limiting production of certain pro-inflammatory cytokines, including TNFα and IL-12.[5]

Vitamin D has been associated with several specific infectious diseases, including Tuberculosis, *Helicobacter pylori* infection, hepatitis C, Influenza, bacterial vaginosis, HIV, Candida albicans infection, and invasive group A streptococcus infection in the skin.[5] Additionally, Vitamin D receptor (VDR) polymorphisms have been linked to tuberculosis,[16] *Mycobacterium malmoense* pulmonary disease,[17] the clinical phenotypes of Hepatitis B infection,[18] leprosy type,[19] the rate of HIV progression to AIDS,[20] and chronic periodinitis.[21]

Panierakis and colleagues found that *Staphyloccoccus aureus* nasal colonization was associated with VDR polymorphisms in a cohort of patients with Type I Diabetes Mellitus,[22] yet, this association was not confirmed in the general population.[23] However, Matheson and colleagues recently demonstrated that vitamin D deficiency is significantly associated with an increased risk of Methicillin-resistant *Staphyloccoccus aureus* (MRSA) nasal carriage compared to individuals with sufficient vitamin D levels. The latter finding indicates that vitamin D deficiency may be a risk factor for MRSA colonization and therefore, potentially for MRSA infection.[24]

Presently, *S. aureus* is implicated in the vast majority of skin and soft tissue infections in humans and also has the potential to cause more serious, life-threatening infections including bacteremia, pneumonia, abscesses, meningitis, osteomyelitis, endocarditis, and sepsis.[14] MRSA, which is resistant to β-lactam antibiotics and other chemotherapeutic agents, was first reported in 1961[25] and has since become problem worldwide in both the clinical and community settings.[26,27,28,29] Approximately 19,000 hospitalized patients in the United States die due to MRSA infections every year, a number similar to the combined number of deaths due to AIDS, tuberculosis, and viral hepatitis.[30] Although the incidence of invasive healthcare-associated MRSA (HA-MRSA) infections has declined in recent years in the United States,[31] MRSA infections in general still seem to be on the rise.[30] The increasing frequency of MRSA infections with unique combinations of resistant traits and virulence factors has complicated treatment and led to high morbidity and mortality.[14,28,30]

High risk groups for community-acquired MRSA (CA-MRSA) infection include HIV positive patients,[32] males, black individuals,[33] persons of age less than 2 or greater than 64,[30,33] young adults, athletes in contact sports, injection drug users, men who have sex with men, military personnel, persons living in correctional facilities, residential homes, or shelters, veterinarians and pig farmers, patients with recent influenza-like illnesses/severe pneumonia or current skin and soft tissue infection, patients with a history or colonization or recent infection with a community-associated MRSA strain, or close contact with a person colonized and/or infected with MRSA.[30] Risk factors for healthcare-

associated MRSA infection include intubation, the presence of an open wound, treatment with antibiotics and/or steroids, all occurring within 24 hours of ICU admission,[34] history of hospitalization, surgery, long-term care residence, MRSA infection or colonization,[33] and lack of use of contact precautions.[35,36] In recent years, however, the distinctions between CA-MRSA and HA-MRSA are beginning to blur as CA-MRSA is now endemic in some US hospitals.[37]

Given that vitamin D contributes to a healthy immune system and new methods for prevention and treatment of MRSA are clearly needed, we sought to determine if vitamin D deficiency was significantly associated with MRSA infection.

METHODS

Study Design and Population

All patients with vitamin D determinations at the Atlanta Veterans Affairs Medical Center (AVAMC) from January, 2007 to August, 2010 were included in the analysis. Data, including age, gender, race, ethnicity, BMI, HIV status, and serum 25(OH)D level were routinely collected from patients. These patients were matched by social security number and last name with an on-going study (October, 2005 through December, 2010) of patients with well characterized MRSA infection. The first recorded serum 25(OH)D level was considered the exposure; any subsequent serum 25(OH)D recordings were discarded. Patients with one or more MRSA infections at any time during the study period were considered cases. Patients with serum 25(OH)D determinations without an MRSA infection served as controls. There were no exclusion criteria. The analyses were carried out under the assumptions that vitamin D levels are fairly constant, outside of the effect of season, and that MRSA infection does not affect serum vitamin D level.

This study was approved by the Emory University Institutional Review Board and the Veterans' Affairs Research and Development Committee.

Determination of MRSA infection

Samples for *S. aureus* culture were collected from the site of infection and processed in the AVAMC laboratory. *S. aureus* was identified by morphology as well as by either the Staphaurex latex agglutination test (Remel, USA) or a positive tube coagulase test. Susceptibility to methicillin was evaluated with a cefoxitin disk-

diffusion test, as described by the Clinical and Laboratory Standards Institute (CLSI) guidelines.[38]

The number of MRSA infections per patient was calculated. MRSA infections were classified according to National Healthcare Safety Network (NHSN) criteria (Horan-NHSN) and the frequency of each classification was determined. Location of the patient at the time of diagnosis (inpatient or outpatient setting) was also recorded.

Determination of Vitamin D Level

A blood sample was collected from all patients and sent to a local Quest Diagnostics laboratory in order to quantify the serum vitamin D level using liquid chromatography/tandem mass spectrometry (LC/MS/MS). LC/MS/MS involves three steps: extraction via protein precipitation, separation via high-performance liquid chromatography (HPLC), and detection and quantification via tandem mass spectrometry. This method is sensitive and equally specific for both $25(OH)D_2$ and $25(OH)D_3$, which are measured and reported separately, then summed to determine total 25(OH)D. The reportable range for $25(OH)D_2$ and $25(OH)D_3$ is 4 - 512 ng/mL. If a patient's 25(OH)D level was reported as "<4," this value was changed to 2 ng/mL for all calculations.

Potential Confounders

Variables evaluated as potential confounders for the relationship between MRSA infection and Vitamin D status included age, race, ethnicity, gender, body

mass index (BMI), and HIV status. Race was defined as black, white, or other. Ethnicity was defined as Hispanic or non-Hispanic.

Statistical Analyses

All statistical analyses were carried out using SAS Version 9.2. The significance level was set a priori at 5%. No observations were excluded.

Descriptive statistics and logistic regression were carried out on three distinct subject groups: the first group included all cases and all controls, the second included cases with skin or soft tissue infection (SSTI) and all controls, and the final group included outpatient cases and all controls. The latter two groups were analyzed in order to investigate whether the association between vitamin D and MRSA infection was more or less pronounced in these subgroups.

A. Bivariate analyses

Bivariate analyses were performed to determine associations between case/control status and potential confounders, as well as between serum 25(OH)D and potential confounders. Serum 25(OH)D level was analyzed as a continuous variable and also as a dichotomous variable (deficient (<20 ng/mL) vs. non-deficient (≥20 ng/mL)). Seasons of vitamin D measurement were defined as follows: winter: December-February, spring: March-May, summer (June-August), and fall (September-October). Continuous variables were evaluated using two sample t-tests and categorical variables were analyzed using χ^2 tests.

Since for many of the subjects there was a long time period between the date of their first vitamin D determination and the date of their MRSA infection, a sensitivity analysis was conducted using only cases for which this time period was less than 150 days.

B. Multivariate logistic regression

Multivariate logistic regression was used to determine the independent association between vitamin D level and case/control status after adjusting for all variables with a p-value <0.2 in the bivariate analyses, as well as variables thought to be clinically relevant regardless of statistical significance. Subjects of black and other race were grouped for the regression because of the small number of subjects in the other race category.

C. Secondary Statistical Analyses

Additionally, all cases were analyzed by site of infection, location (inpatient or outpatient) of positive culture, and season of infection. The same season definitions were used for infection as were used for vitamin D measurement (winter: December-February, spring: March-May, summer: June-August, and fall: September-October). Infections that occurred in 2005 were excluded from this analysis, since infections were only recorded for part of this year. Because the first serum 25(OH)D level measured for each patient was used in the analysis, and each case did not simultaneously present with an MRSA infection, the number of days between positive MRSA culture (day 0) and serum 25(OH)D recording was determined. In addition,

all vitamin D determinations in the database were used to calculate the median serum 25(OH)D for all subjects by year.

Because the patient population at the VAMC is not necessarily representative of the general population, additional analyses were carried out in order to further characterize the patients included in the study. Both age and race were analyzed by the other patient characteristics.

RESULTS

A. Bivariate Analyses

A total of 6405 patients with vitamin D determinations were included in the analyses (**Table I**). The mean (*SD*) age of the sample was 64.2 (*14.4*). The cohort was mostly male (88.6%). Half of the subjects identified as black (n=3200; 50%) and almost half identified as white (n=3146; 49.1%). A very small percent (n=57; 0.9%) identified as neither black nor white. Very few subjects were Hispanic (n=47; 0.7%). The mean (*SD*) BMI was 26.9 (*5.6*) and the majority of subjects fell into the overweight BMI category (n=2334; 36.6). HIV positive subjects comprised 15% (n=960) of the group. Slightly less than half (n= 2618; 40.9%) of patients were deficient in 25(OH)D (serum 25(OH)D level <20 ng/mL).

In the entire cohort, 401 (6.3%) subjects experienced at least one MRSA infection during the study period. MRSA infection was significantly associated with younger age (p=0.0008), male gender (p=0.0023), lower BMI (p<0.0001), HIV positive status (p<0.0001), and vitamin D deficiency (p<0.0001) in the bivariate analyses. Mean (*SD*) 25(OH)D levels in ng/mL were 21.1 (*12.4*) and 24.0 (*12.6*) for cases and controls, respectively. Race and ethnicity were not significantly associated with MRSA infection.

In addition to MRSA infection, 25(OH)D level was significantly associated with age, gender, race, BMI, season of measurement, and HIV status (**Table II**). Vitamin D deficiency was significantly associated with younger age (p<0.0001), female gender (p=0.0078), and HIV positive status (p<0.0001). The majority of black subjects (55.8%) were deficient in 25(OH)D, approximately half (49.1%) of other

race subjects were deficient, and only 25.5% of white subjects were deficient ($p<0.0001$). Serum 25(OH)D varied significantly across BMI, although there was no direct relationship. Of the underweight individuals, 47.4% were 25(OH)D deficient. This frequency of deficiency was followed closely by obese individuals (46.1%). Normal BMI and overweight individuals had the lowest frequencies of deficiency (40.1% and 37.0%, respectively). Ethnicity was not significantly associated with 25(OH)D level. Frequency of deficiency was highest in the winter (49.9%), followed by the spring (41.8%). Frequency of deficiency was lowest in the summer (32.9%), followed by the fall (38.1%). Subject characteristics and bivariate analyses using the SSTI and outpatient cases subgroups can be found in Tables III-VI.

Seventy-five patients experienced an MRSA infection within 150 days of their first serum 25(OH)D determination. Mean (*SD*) serum 25(OH)D level for cases (19.6 (*13.3*)) was found to be significantly lower than that of controls (24.03 (*12.6*)) ($p=0.0025$).

B. Multivariate Logistic Regression

The multivariate logistic regression model using all cases confirmed significant independent associations for male gender, white race vs. black/other race, BMI, HIV positive status, and 25(OH)D deficiency (**Table VII**). Patients with MRSA infections were more likely to be underweight and least likely to be overweight. The odds ratio for serum 25(OH)D deficiency (<20 ng/mL) vs. non-deficiency (≥20 ng/mL) was 1.63 (95% confidence interval (CI): 1.31, 2.03).

Subgroup analyses using only SSTIs and only outpatient cases also identified serum 25(OH)D level as an independent risk factor for MRSA infection, although in the former model the association only trended towards significance (**Table VII**). The odds ratios for serum 25(OH)D deficiency vs. non-deficiency were 1.28 (95% CI: 0.97, 1.70) and 1.67 (95% CI: 1.33, 2.09) for SSTIs only and outpatient cases only, respectively.

C. Secondary Statistical Analyses

Most cases (70.1%) experienced one infection while relatively small percentages of cases experienced 2 to 5 infections over the duration of the study period (**Figure 1**). The most common site of MRSA infection was skin and soft tissue (n=232; 57.9%), followed by genitourinary tract (n=53; 13.2%), bloodstream and cardiovascular system (n=37; 9.2%), respiratory (n=32; 8.0%), bone and joint (n=22; 5.5%), surgical site (n=13; 3.2%), eye/ear/nose/throat/mouth (n=10; 2.5%), reproductive tract (n=1; 0.3%), and gastrointestinal tract (n=1; 0.3%) (**Figure 2**). Almost all of the MRSA infections were diagnosed in the outpatient setting (n=366; 91.3%) as opposed to the inpatient setting (n=35, 9%). There was no significant difference in frequency of infection by season (p=0.1343) (**Table VIII**).

The number of days between vitamin D determination and positive MRSA culture ranged from 1669 days (approximately 4.57 years) before infection to 1360 days (3.72 years) after the infection with a median of 77 days prior to infection (**Figure 3**). Median vitamin D levels were approximately the same from 2007 to 2009, and then dropped significantly to 19 ng/mL in 2010 ($p<0.0001$) (**Table IX**).

In this group of veterans, males were significantly older than females ($p<0.0001$), white subjects were significantly older than black subjects and subjects in the "other race" category ($p<0.0001$), and non-Hispanics were significantly older than Hispanics ($p=0.0308$) (**Table X**). BMI related inversely to age ($p<0.0001$). HIV positive individuals were significantly younger than HIV negative subjects ($p<0.0001$). Race was significantly associated with gender ($p<0.0001$), ethnicity ($p<0.0001$), and HIV status ($p<0.0001$) (**Table XI**). The other race category was comprised of the highest percentage of females (29.8%) and Hispanic subjects (7.0%). Of the black subjects, 23.2% were HIV positive, which was significantly more than in the white and other race categories (6.9% and 0.0%, respectively).

DISCUSSION

Our findings suggest that an association exists between MRSA infection and vitamin D deficiency in our patients at the AVAMC, and the relationship remained even when adjusting for age, gender, race, ethnicity, BMI, and HIV status. This association was observed when including all cases in the analyses as well as when including only outpatient cases. The model using only SSTIs revealed an association as well but it only trended towards significance, likely because of the small number of cases in this group.

The association between vitamin D deficiency and MRSA infection is very plausible since each known role that vitamin D plays in immunity is applicable in the defense against *S. aureus.* Vitamin D aids in reinforcing the physical barrier formed by epithelial cells, which is the first line of defense against all invading organisms. At the body's epithelia, organisms meet a number of antimicrobial peptides, including vitamin D-dependent hBD2 and cathelicidin, which are induced by exposure to *S. aureus*.[13] Clinical isolates of methicillin-susceptible *S. aureus* (MSSA) and MRSA strains significantly increase production of hBD2 (>10-fold); however hBD2 has only weak gram positive antimicrobial activity in general and *S. aureus* has proven resistant to high concentrations of hBD-2.[13,14,39] Nagaoka and colleagues showed that certain defensins work synergistically with cathelicidin against S. aureus by augmenting the membrane permeabilization of target cells,[40] so perhaps the purpose of hBD2 is to aid cathelicidin, rather than to defend against *S. aureus* on its own. In contrast to hBD2, cathelicidin has potent bactericidal activity against *S. aureus.* Komatsuzawa and colleagues demonstrated that cathelicidin has dose-dependent activity against *S. aureus* and that even low-susceptibility MRSA strains succumb to high concentrations of cathelicidin and hBD3

together.[13] Some MRSA strains, however, have begun to show increased resistance to cathelicidin alone.[41]

Upon invading the body, pathogens are recognized by "Toll-like receptors" which are expressed on the surfaces of many cells including keratinocytes, Langerhans cells, monocytes/macrophages, dendritic cells, mast cells, endothelial cells, fibroblasts and adipocytes.[42] TLR2, which has been named one of the most factors in the defense against S. aureus,[43] recognizes and binds the peptidoglycan, lipopeptides, and lipoteichoic acid on *S. aureus* and subsequently activates a number of internal cell signaling pathways, one of which includes induction of 1α-hydroxylase and results in the production of active Vitamin D. Active vitamin D then binds and activates the VDR in monocytes and neutrophils, resulting in the expression of catheicidin.[44,45] Vitamin D also contributes to monocyte killing by oxidative burst, a method which is used for killing *S. aureus*.[14]

As expected based on previous literature, the odds of male gender[33] and HIV positive status[32] were increased among MRSA cases in our multivariate regression model. In contrast with a recent large epidemiologic study which uncovered higher incidence of MRSA infections in black individuals,[33] our study revealed that patients with black or other race were less likely than white patients to experience an MRSA infection. This finding could be due to the fact that we controlled for vitamin D status. To our knowledge, there is no known association between MRSA infection and BMI. We found that individuals with MRSA infections were more likely to be underweight and least likely to be overweight. This finding may be related poor nutritional status or chronic illness, as patients who are underweight are often afflicted by these conditions;

furthermore, poor nutritional status and chronic illness may predispose patients to MRSA infection.

Our analysis revealed that vitamin D deficiency was significantly associated with younger age, which is opposite from national trends.[8] This finding can be explained by the makeup of our veteran population, since black and female veterans tend to be younger, and these two groups had higher frequencies of vitamin D deficiency. There were also higher frequencies of deficiency in the obese and underweight groups. Reduced bioavailability is a known cause of vitamin D deficiency in obesity,[1] and the underweight subjects included in the analysis may have been malnourished or chronically ill, which have known associations with vitamin D deficiency as well.[1,46]

According to our data, baseline vitamin D levels in our patient population at the AVAMC have recently decreased. As expected, our results revealed a clear predominance of vitamin D deficiency in the winter followed by the spring, which is in concordance with the potency of the sun in Georgia. MRSA infection, on the other hand, did not follow this trend. Although the difference in infection by season was not significant, the frequency of MRSA infection was slightly higher in the spring, followed by the fall. Other studies conducted in Georgia have shown MRSA infection peaks in mid-summer to mid-fall (July through October).[47,48] This variation in peak season is not surprising, as many factors contribute to infection with MRSA.

In concordance with the general population, the Veteran's Affairs Healthcare System has witnessed a significant increase in the incidence rate of MRSA infection over the past 8 years.[49] Additionally, vitamin D deficiency has been linked to adverse health outcomes and significantly increased healthcare expenditures in Veterans with *S. aureus*

infections.[50] Clearly, methods for combating MRSA infection are needed for the veteran and general populations and vitamin D deficiency may be an easily modifiable risk factor. Vitamin D may possibly even be useful as an adjunctive therapy to treat MRSA infections, as it has shown some promise in the treatment of other infectious diseases.[51] (yamshchikov).

Strengths and limitations:

Strengths

We used a large sample size and a very complete dataset. Our study is very unique, as there is currently no published literature on this association. Our findings are applicable to current practice at the AVAMC and will inspire further investigation into this topic.

Limitations

We lacked information about certain potential confounders of the relationship between MRSA infection and vitamin D deficiency including hospitalization history, recent medications, current living situation, occupation, recreational activities, and comorbidies (other than HIV). Therefore, we could not control for these potential confounders in our analyses.

The analytical sensitivity for our measure of serum 25(OH)D was 4 ng/mL, and measurements of many of our patients registered as "<4." By replacing this value with "2" so that we could carry out our analyses may have over- or underestimated mean/median values and relationships with vitamin D status. Furthermore, because the role of vitamin D in immune function has yet to be completely elucidated, we

used the deficiency cut point established based on current data for other health conditions, which may not be the ideal cut point to use when evaluating immune function. We made the assumption that vitamin D levels were fairly constant over time, outside of the known effect of season. Because we used first vitamin D level as our exposure, we are unable to comment on the temporal relationship between vitamin D deficiency and MRSA infection, and some of our data points were collected years apart for the same patient. We purposely used the first vitamin D level to exclude the effect of vitamin D supplementation. The persistent effect of vitamin D deficiency and MRSA infection in the subgroup with data available within 150 days supports our assumptions.

Lastly, the AVAMC patient population is not necessarily representative of the general population and therefore our results have limited generalizability.

Future directions

A study similar to this one should be carried out in a more diverse population in order to investigate if our findings can be replicated. The cross-sectional design of our study only allows us to make statements about association and not causation. Further research is necessary in order to explore if causation exists and to determine if correcting vitamin D levels through supplementation may reduce rates of infection with MRSA. Future studies should also investigate whether using vitamin D as an adjunctive therapy in the treatment of MRSA infection can improve health outcomes and reduce healthcare expenditures.

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Table I. Subject Characteristics *(all cases and controls)*

	Cases		Controls		Total		p-value
	Mean or N	*(SD or %)*	*Mean or N*	*(SD or %)*	*Mean or N*	*(SD or %)*	
Total	401	*(6.3)*	6004	*(93.7)*	6405	*(100)*	
Age							
(Mean (SD))	60.0	*(14.9)*	62.5	*(14.6)*	62.3	*(14.7)*	0.0008**
***Age Groups** (n(%))*							
<50	102	*(25.4)*	1142	*(19.0)*	1244	*(19.4)*	0.0046**
50-69	189	*(47.1)*	2936	*(48.9)*	3125	*(48.8)*	
≥70	110	*(27.4)*	1926	*(32.1)*	2036	*(31.8)*	
Gender (n(%)							
Male	374	*(93.3)*	5299	*(88.3)*	5673	*(88.6)*	0.0023**
Female	27	*(6.7)*	705	*(11.7)*	732	*(11.4)*	
Race (n(%))							
Black	209	*(52.1)*	2991	*(49.8)*	3200	*(50.0)*	0.5725
White	190	*(47.4)*	2956	*(49.3)*	3146	*(49.1)*	
Other	2	*(0.5)*	55	*(0.92)*	57	*(0.9)*	
Ethnicity (n(%))							
Hispanic	4	*(1.0)*	43	*(0.72)*	47	*(0.7)*	0.5365
Non-Hispanic	397	*(99.0)*	5961	*(99.3)*	6358	*(99.3)*	
BMI*							
(Mean (SD))	25.6	*(6.5)*	27.0	*(5.5)*	26.9	*(5.6)*	<0.0001**
***BMI Level** (n(%))*							
Underweight	35	*(8.7)*	231	*(3.9)*	266	*(4.2)*	<0.0001**
Normal	169	*(42.1)*	1885	*(31.5)*	2054	*(32.2)*	
Overweight	112	*(27.9)*	2222	*(37.2)*	2334	*(36.6)*	
Obese	85	*(21.2)*	1643	*(27.5)*	1728	*(27.1)*	
HIV Status (n(%))							
Positive	115	*(28.7)*	845	*(14.1)*	960	*(15.0)*	<0.0001**
Negative	286	*(71.3)*	5159	*(85.9)*	5445	*(85.0)*	
Vitamin D (ng/mL)							
Mean (SD)	21.1	*(12.4)*	24.0	*(12.6)*	23.8	*(12.6)*	<0.0001**
***Vitamin D Level** (n(%))*							
<20	211	*(52.6)*	2407	*(40.1)*	2618	*(40.9)*	<0.0001**
≥20	190	*(47.4)*	3597	*(59.9)*	3787	*(59.1)*	

*BMI: ((weight(lbs)*703)/(height(in)^2)); BMI Levels: Underweight= <18.5; Normal= 18.5-24.99; Overweight= 25-29.99; Obese = >30

**Significant

Note: 23 BMI observations were missing; 2 race observations were missing

Table II. Vitamin D levels by patient characteristics and season of measurement *(all cases and controls)*

	Vitamin D (ng/mL)						p-value
	<20		20-29		≥30		
	n	***(%)***	**n**	***(%)***	**n**	***(%)***	
Total	2618	*(40.9)*	1902	*(29.7)*	1885	*(29.4)*	<0.0001**
Age (years)							
(Mean (SD))	59.2	*(14.6)*	63.6	*(14.8)*	65.5	*(13.8)*	<0.0001**
Age Groups							
<50	660	*(53.1)*	344	*(27.7)*	240	*(19.3)*	<0.0001**
50-69	1328	*(42.5)*	880	*(28.2)*	917	*(29.3)*	
≥70	630	*(30.9)*	678	*(35.7)*	728	*(35.8)*	
Gender							
Male	2280	*(40.2)*	1701	*(30.0)*	1692	*(29.8)*	0.0078**
Female	338	*(46.2)*	201	*(27.5)*	193	*(26.4)*	
Race							
Black	1789	*(55.9)*	893	*(27.9)*	518	(16.2)	<0.0001**
White	800	*(25.4)*	994	*(31.6)*	1352	*(43.0)*	
Other	28	*(49.1)*	15	*(26.3)*	14	*(24.6)*	
Ethnicity							
Hispanic	20	*(42.6)*	15	*(31.9)*	12	*(25.5)*	0.8371
Non-Hispanic	2598	*(40.9)*	1887	*(29.7)*	1873	*(29.5)*	
BMI*							
(Mean (SD))	27.3	*(6.2)*	29.9	*(5.3)*	26.3	*(5.0)*	<0.0001**
BMI Level							
Underweight	126	*(47.4)*	75	*(28.2)*	65	*(24.4)*	<0.0001**
Normal	824	*(40.1)*	572	*(27.9)*	658	*(32.0)*	
Overweight	865	*(37.0)*	739	*(31.7)*	730	*(31.3)*	
Obese	796	*(46.1)*	509	*(29.5)*	423	*(24.5)*	
Season[†]							
Winter	784	*(49.9)*	429	*(27.3)*	357	*(22.7)*	<0.0001**
Spring	834	*(41.8)*	597	*(29.9)*	565	*(28.3)*	
Summer	520	*(32.9)*	524	*(33.2)*	536	*(33.9)*	
Fall	480	*(38.1)*	352	*(28.0)*	427	*(33.9)*	
HIV Status							
Positive	507	*(*52.8)	267	*(*27.8)	186	*(19.4)*	<0.0001**
Negative	2111	*(*38.8)	1635	(30.0)	1699	*(31.2)*	

*BMI: ((weight(lbs)*703)/(height(in)^2)); BMI Levels: Underweight= <18.5; Normal= 18.5-24.99; Overweight= 25-29.99; Obese = >30

[†]Indicates season when Vitamin D level was tested. Seasons were defined as: Winter= December-February; Spring= March-May; Summer= June-August; Fall= September-October

**Significant

Note: 23 BMI observations were missing; 2 race observations were missing

Table III. Subject Characteristics *(cases with skin and soft tissue infection and controls)*

	Cases		Controls		Total		p-value
	Mean or N	*(SD or %)*	*Mean or N*	*(SD or %)*	*Mean or N*	*(SD or %)*	
Total	232	*(3.7)*	6004	*(96.3)*	6236	*(100)*	
Age							
(Mean (SD))	56.0	*(13.6)*	64.5	*(14.3)*	62.3	*(14.7)*	<0.0001**
***Age Groups** (n(%))*							
<50	76	*(32.8)*	1142	*(19.0)*	1218	*(19.5)*	<0.0001**
50-69	114	*(49.1)*	2936	*(48.9)*	3050	*(48.9)*	
≥70	42	*(18.1)*	1926	*(32.1)*	1968	*(31.6)*	
Gender (n(%)							
Male	212	*(91.4)*	5299	*(88.3)*	5511	*(88.4)*	0.1455
Female	20	*(8.6)*	705	*(11.7)*	725	*(11.6)*	
Race (n(%))							
Black	131	*(56.5)*	2991	*(49.8)*	3122	*(50.1)*	0.1394
White	99	*(42.7)*	2956	*(49.3)*	3055	*(49.1)*	
Other	2	*(0.9)*	55	*(0.92)*	57	*(0.9)*	
Ethnicity (n(%))							
Hispanic	3	*(1.3)*	43	*(0.72)*	46	*(0.7)*	0.2440
Non-Hispanic	229	*(98.7)*	5961	*(99.3)*	6190	*(99.3)*	
BMI*							
(Mean (SD))	26.6	*(6.8)*	27.0	*(5.5)*	27.0	*(5.6)*	0.3960
***BMI Level** (n(%))*							
Underweight	11	*(4.7)*	231	*(3.9)*	242	*(3.9)*	0.0509
Normal	91	*(39.2)*	1885	*(31.5)*	1976	*(31.8)*	
Overweight	70	*(30.2)*	2222	*(37.2)*	2292	*(36.9)*	
Obese	60	*(25.9)*	1643	*(27.5)*	1703	*(27.4)*	
HIV Status (n(%))							
Positive	90	*(38.8)*	845	*(14.1)*	935	*(14.9)*	<0.0001**
Negative	142	*(61.2)*	5159	*(85.9)*	5301	*(85.0)*	
Vitamin D (ng/mL)							
Mean (SD)	21.8	*(12.3)*	24.0	*(12.6)*	24.0	*(12.6)*	0.0087**
***Vitamin D Level** (n(%))*							
<20	116	*(50.0)*	2407	*(40.1)*	2523	*(40.5)*	0.0025**
≥20	116	*(50.0)*	3597	*(59.9)*	3713	*(59.5)*	

*BMI: ((weight(lbs)*703)/(height(in)^2)); BMI Levels: Underweight= <18.5; Normal= 18.5-24.99; Overweight= 25-29.99; Obese = >30

**Significant

Note: 23 BMI observations were missing; 2 race observations were missing

Table IV. Vitamin D levels by patient characteristics and season of measurement ***(cases with skin and soft tissue infection and controls)***

	Vitamin D (ng/mL)						p-value
	<20		20-29		≥30		
	n	***(%)***	**n**	***(%)***	**n**	***(%)***	
Total	2523	*(40.5)*	1860	*(29.8)*	1853	*(29.7)*	<0.0001**
Age (years)							
(Mean (SD))	59.1	*(14.5)*	63.4	*(14.9)*	65.4	*(13.8)*	<0.0001**
Age Groups							
<50	642	*(52.7)*	341	*(28.0)*	235	*(19.3)*	<0.0001**
50-69	1283	*(42.0)*	861	*(28.2)*	906	*(29.7)*	
≥70	598	*(30.4)*	658	*(33.4)*	712	*(36.2)*	
Gender							
Male	2189	*(39.7)*	1662	*(30.2)*	1660	*(30.1)*	0.0078**
Female	334	*(46.1)*	198	*(27.3)*	193	*(26.6)*	
Race							
Black	1729	*(55.4)*	880	*(28.2)*	513	*(16.4)*	<0.0001**
White	765	*(25.0)*	965	*(31.6)*	1325	*(43.4)*	
Other	28	*(49.1)*	15	*(26.3)*	14	*(24.6)*	
Ethnicity							
Hispanic	19	*(41.3)*	15	*(32.6)*	12	*(26.1)*	0.8463
Non-Hispanic	2504	*(40.5)*	1845	*(29.8)*	1841	*(29.7)*	
BMI*							
(Mean (SD))	27.4	*(6.2)*	27.0	*(5.2)*	26.3	*(5.0)*	<0.0001**
BMI Level							
Underweight	112	*(46.3)*	66	*(27.3)*	64	*(26.5)*	<0.0001**
Normal	783	*(39.6)*	554	*(28.0)*	639	*(32.3)*	
Overweight	841	*(36.7)*	729	*(31.8)*	722	*(31.5)*	
Obese	780	*(45.8)*	504	*(29.6)*	419	*(24.6)*	
Season[†]							
Winter	756	*(49.7)*	415	*(27.3)*	350	*(23.0)*	<0.0001**
Spring	803	*(41.1)*	591	*(30.3)*	558	*(28.6)*	
Summer	496	*(32.4)*	509	*(33.3)*	526	*(34.4)*	
Fall	468	*(38.0)*	345	*(28.0)*	419	*(34.0)*	
HIV Status							
Positive	493	*(*52.7)	262	*(*28.0)	180	*(19.3)*	<0.0001**
Negative	2030	*(*38.3)	1598	(30.2)	1673	*(31.6)*	

*BMI: ((weight(lbs)*703)/(height(in)^2)); BMI Levels: Underweight= <18.5; Normal= 18.5-24.99; Overweight= 25-29.99; Obese = >30

[†]Indicates season when Vitamin D level was tested. Seasons were defined as: Winter= December-February; Spring= March-May; Summer= June-August; Fall= September-October

**Significant

Note: 23 BMI observations were missing; 2 race observations were missing

Table V. Subject Characteristics *(outpatient cases and controls)*

	Cases		**Controls**		**Total**		**p-value**
	Mean or N	*(SD or %)*	*Mean or N*	*(SD or %)*	*Mean or N*	*(SD or %)*	
Total	366	*(5.8)*	6004	*(94.3)*	6370	*(100)*	
Age							
(Mean (SD))	59.4	*(15.0)*	62.5	*(14.6)*	62.3	*(14.7)*	<0.0001**
***Age Groups** (n(%))*							
<50	99	*(26.2)*	1142	*(14.5)*	1241	*(19.5)*	0.0004**
50-69	171	*(46.7)*	2936	*(48.9)*	3107	*(48.8)*	
≥70	96	*(26.2)*	1926	*(32.1)*	2022	*(31.7)*	
Gender (n(%)							
Male	340	*(92.9)*	5299	*(88.3)*	5639	*(88.5)*	0.0069**
Female	26	*(7.1)*	705	*(11.7)*	731	*(11.5)*	
Race (n(%))							
Black	193	*(52.7)*	2991	*(49.8)*	3184	*(50.0)*	0.5735
White	171	*(46.7)*	2956	*(49.3)*	3127	*(49.1)*	
Other	2	*(0.6)*	55	*(0.92)*	57	*(0.9)*	
Ethnicity (n(%))							
Hispanic	4	*(1.1)*	43	*(0.72)*	47	*(0.7)*	0.3450
Non-Hispanic	362	*(98.9)*	5961	*(99.3)*	6323	*(99.3)*	
BMI*							
(Mean (SD))	26.1	*(6.5)*	27.0	*(5.5)*	26.9	*(5.6)*	0.0116**
***BMI Level** (n(%))*							
Underweight	24	*(6.6)*	231	*(3.9)*	255	*(4.0)*	<0.0001**
Normal	149	*(40.7)*	1885	*(31.5)*	2034	*(32.1)*	
Overweight	109	*(29.8)*	2222	*(37.2)*	2331	*(36.7)*	
Obese	84	*(23.0)*	1643	*(27.5)*	1727	*(27.2)*	
HIV Status (n(%))							
Positive	110	*(30.1)*	845	*(14.1)*	955	*(15.0)*	<0.0001**
Negative	256	*(70.0)*	5159	*(85.9)*	5415	*(85.0)*	
Vitamin D (ng/mL)							
Mean (SD)	21.1	*(12.4)*	24.0	*(12.6)*	23.9	*(12.6)*	<0.0001**
***Vitamin D Level** (n(%))*							
<20	195	*(53.3)*	2407	*(40.1)*	2602	*(40.9)*	<0.0001**
≥20	171	*(46.7)*	3597	*(59.9)*	3768	*(59.2)*	

*BMI: ((weight(lbs)*703)/(height(in)^2)); BMI Levels: Underweight= <18.5; Normal= 18.5-24.99; Overweight= 25-29.99; Obese = >30

**Significant

Note: 23 BMI observations were missing; 2 race observations were missing

Table VI. Vitamin D levels by patient characteristics and season of measurement *(outpatient cases and controls)*

	Vitamin D (ng/mL)						p-value
	<20		20-29		≥30		
	n	***(%)***	**n**	***(%)***	**n**	***(%)***	
Total	2602	*(40.9)*	1892	*(29.7)*	1876	*(29.5)*	<0.0001**
Age (years)							
(Mean (SD))	59.2	*(14.6)*	63.5	*(14.9)*	65.4	*(13.8)*	<0.0001**
Age Groups							
<50	657	*(52.9)*	344	*(27.7)*	240	*(19.3)*	<0.0001**
50-69	1318	*(42.4)*	873	*(28.1)*	916	*(29.5)*	
≥70	627	*(31.0)*	675	*(33.4)*	720	*(35.6)*	
Gender							
Male	2264	*(40.2)*	1692	*(30.0)*	1683	*(29.9)*	0.0067**
Female	338	*(46.2)*	200	*(27.4)*	193	*(26.4)*	
Race							
Black	1776	*(55.8)*	890	*(28.0)*	518	*(16.3)*	<0.0001**
White	797	*(25.5)*	987	*(31.6)*	1343	*(43.0)*	
Other	28	*(49.1)*	15	*(26.3)*	14	*(24.6)*	
Ethnicity							
Hispanic	20	*(42.6)*	15	*(31.9)*	12	*(25.5)*	0.8358
Non-Hispanic	2582	*(40.9)*	1877	*(29.7)*	1864	*(29.5)*	
BMI*							
(Mean (SD))	27.3	*(6.2)*	27.0	*(5.2)*	26.3	*(5.0)*	<0.0001**
BMI Level							
Underweight	119	*(46.7)*	71	*(27.8)*	65	*(25.5)*	<0.0001**
Normal	817	*(40.2)*	566	*(27.8)*	651	*(32.0)*	
Overweight	863	*(37.0)*	739	*(31.7)*	729	*(31.3)*	
Obese	796	*(46.1)*	509	*(29.5)*	422	*(24.4)*	
Season[†]							
Winter	784	*(50.1)*	427	*(27.3)*	354	*(22.6)*	<0.0001**
Spring	823	*(41.5)*	595	*(30.0)*	564	*(28.5)*	
Summer	517	*(32.9)*	520	*(33.1)*	535	*(34.0)*	
Fall	478	*(38.2)*	350	*(28.0)*	423	*(33.8)*	
HIV Status							
Positive	503	*(*52.7)	266	*(*27.9)	186	*(19.5)*	<0.0001**
Negative	2099	*(*38.8)	1626	(30.0)	1690	*(31.2)*	

*BMI: ((weight(lbs)*703)/(height(in)^2)); BMI Levels: Underweight= <18.5; Normal= 18.5-24.99; Overweight= 25-29.99; Obese = >30

[†]Indicates season when Vitamin D level was tested. Seasons were defined as: Winter= December-February; Spring= March-May; Summer= June-August; Fall= September-October

**Significant

Note: 23 BMI observations were missing; 2 race observations were missing

Table VII. Logistic Regression Results

	Odds Ratio	95% Confidence Interval
All cases and controls		
Age	0.99	0.98 – 1.00
Gender		
Male	1.70	1.11 – 2.59**
Female	1.00	--
Race		
Black/Other	0.74	0.59 – 0.94**
White	1.00	--
BMI		
Underweight	1.85	1.25 – 2.75**
Normal	1.00	--
Overweight	0.58	0.45 – 0.74**
Obese	0.59	0.45 – 0.78**
HIV Status		
Positive	2.08	1.58 – 2.73**
Negative	1.00	--
Vitamin D Status (ng/mL)		
<20	1.63	1.31 – 2.03**
≥20	1.00	--
Cases with SSTI and controls		
Age	0.98	0.97 – 0.99**
Gender		
Male	1.38	0.84 – 2.28
Female	1.00	--
Race		
Black/Other	0.77	0.57 – 1.04
White	1.00	--
BMI		
Underweight	1.26	0.66 – 2.42
Normal	1.00	--
Overweight	0.68	0.49 – 0.94**
Obese	0.81	0.57 – 1.14
HIV		
Positive	2.85	2.04 – 3.97**
Negative	1.00	--
Vitamin D Status (ng/mL)		
<20	1.28	0.97 – 1.70
≥20	1.00	--
Outpatient cases and controls		
Age	0.99	0.98 – 0.99**
Gender		
Male	1.62	1.05 – 2.50**
Female	1.00	--
Race		
Black/Other	0.74	0.58 – 0.94**
White	1.00	--
BMI		
Underweight	1.46	0.92 – 2.32
Normal	1.00	--

Table VII. Logistic Regression Results (continued)

Overweight	0.64	0.50 – 0.83**
Obese	0.67	0.50 – 0.89**
HIV		
Positive	2.18	1.64 – 2.90**
Negative	1.00	--
Vitamin D Status (ng/mL)		
<20	1.67	1.33 – 2.09**
≥20	1.00	--

*BMI: ((weight(lbs)*703)/(height(in)^2))
BMI Levels: Underweight= <18.5; Normal= 18.5-24.99; Overweight= 25-29.99; Obese = >30
**Significant

Note: 23 BMI observations were missing; 2 race observations were missing

Table VIII. Season of MRSA Infection

Season	MRSA Infections		p-value
	n	*(%)*	
Spring	113	*(28.2)*	0.1343
Summer	87	*(21.7)*	
Fall	111	*(27.7)*	
Winter	90	*(22.4)*	

Seasons were defined as: Winter= December-February; Spring= March-May; Summer= June-August; Fall= September-October

Note: Infections that occurred in 2005 were excluded from this analysis, since infections were only recorded for part of this year.

Table IX. Serum Vitamin D Levels by Year (ALL VITAMIN Ds)

		Vitamin D			p-value
	n	Median	Mean	*(SD)*	
2007	2059	26	27.0	*(16.3)*	<0.0001**
2008	3888	26	26.1	*(12.1)*	
2009	5129	26	27.0	*(12.2)*	
2010	348	19	19.9	*(10.3)*	

**Significant

Note: Vitamin D determinations included in the study were collected from January, 2007 to August, 2010.

Table X. Patient characteristics by Age *(all cases and controls)*

	Age (years) Mean	*(SD)*	p-value
Gender			
Male	66.1	*(13.6)*	<0.0001**
Female	50.8	*(12.8)*	
Race			
Black	59.4	*(14.1)*	<0.0001**
White	68.3	*(13.3)*	
Other	59.3	*(15.2)*	
Ethnicity			
Hispanic	58.9	*(15.3)*	0.0308**
Non-Hispanic	64.2	*(14.4)*	
BMI*			
Underweight	67.1	*(13.1)*	<0.0001**
Normal	66.7	*(15.1)*	
Overweight	64.7	*(14.3)*	
Obese	60.0	*(12.9)*	
HIV Status			
Positive	45.9	*(8.1)*	<0.0001**
Negative	64.5	*(14.3)*	

*BMI: ((weight(lbs)*703)/(height(in)^2)); BMI Levels: Underweight= <18.5; Normal= 18.5-24.99; Overweight= 25-29.99; Obese = >30

**Significant

Table XI. Patient Characteristics by Race

	Black		White		Other		p-value
	n	*(%)*	n	(%)	n	*(%)*	
Gender							
Male	2694	*(84.6)*	2903	*(92.8)*	40	*(70.2)*	<0.0001**
Female	490	*(15.4)*	224	*(7.2)*	17	*(29.8)*	
Ethnicity							
Hispanic	9	*(0.3)*	34	*(1.1)*	4	*(7.0)*	<0.0001**
Non-Hispanic	3175	*(99.7)*	3093	*(98.9)*	53	*(93.0)*	
BMI*							
Underweight	135	*(4.2)*	129	*(4.1)*	2	*(3.5)*	0.2128
Normal	1055	*(33.0)*	983	*(31.4)*	14	*(24.6)*	
Overweight	1122	*(35.0)*	1191	*(38.1)*	21	*(36.8)*	
Obese	882	*(27.6)*	826	*(26.4)*	20	*(35.1)*	
HIV Status							
Positive	738	*(23.2)*	215	*(6.9)*	0	*(0.0)*	<0.0001**
Negative	2446	*(76.8)*	2912	*(93.1)*	57	*(100.0)*	

*BMI: ((weight(lbs)*703)/(height(in)^2)); BMI Levels: Underweight= <18.5; Normal= 18.5-24.99; Overweight= 25-29.99; Obese = >30

**Significant

Figure 1. Number of MRSA infections per case

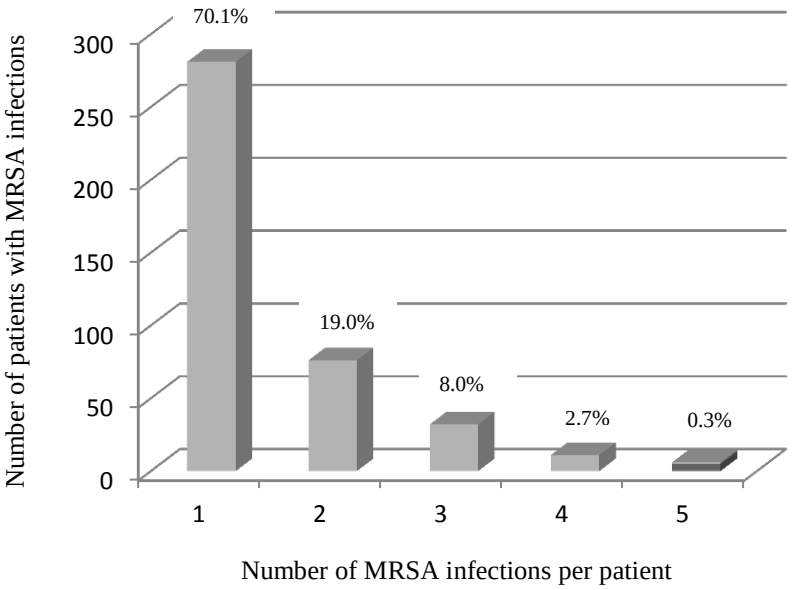

Figure 2. Site of MRSA infection

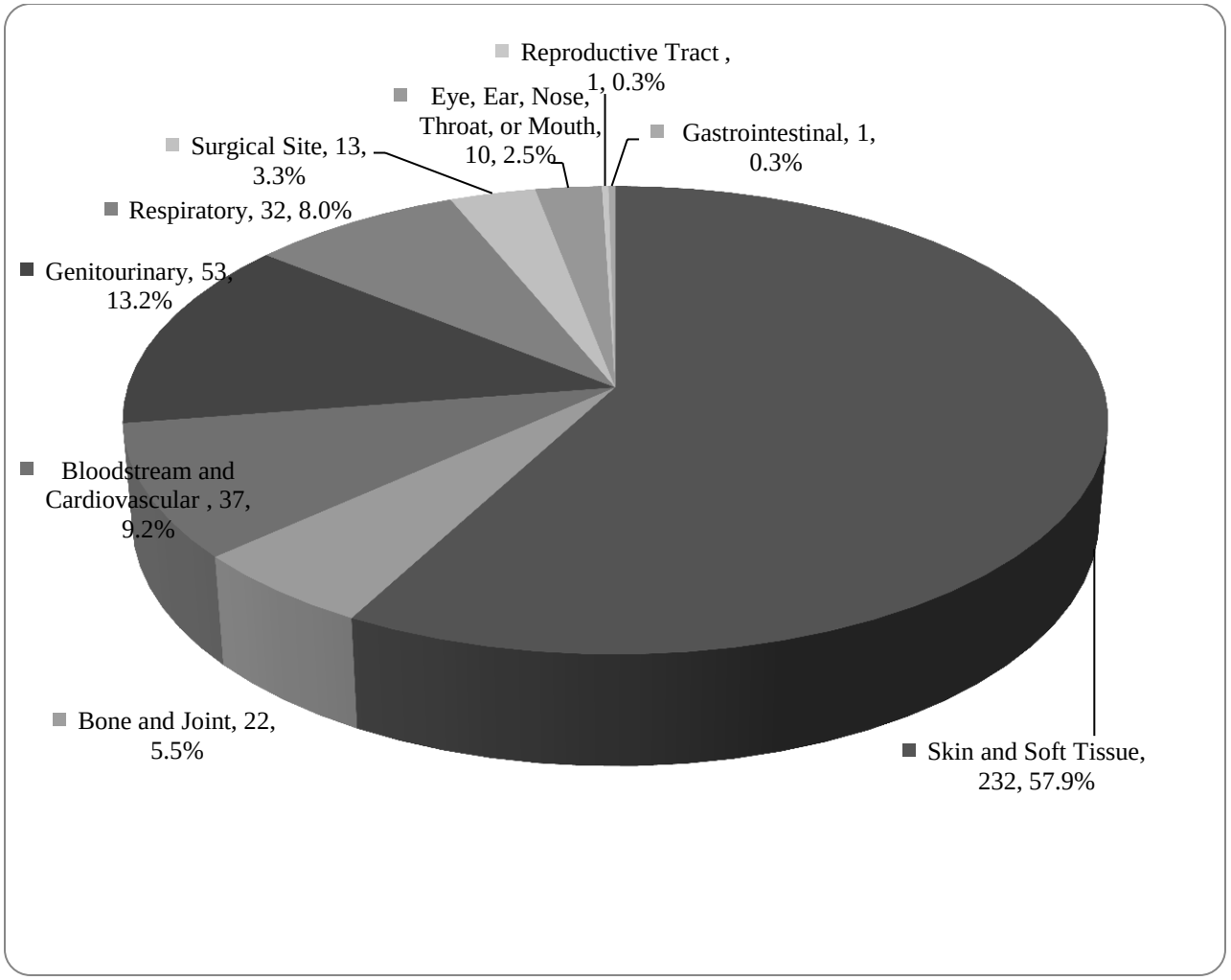

Figure 3. Number of Days Between Serum 25(OH)D Recording and Positive MRSA Culture