Epidemiol. Infect. (2010), **138**, 1322–1327.
doi:10.1017/S0950268809991543

Healthcare costs of *Staphylococcus aureus* and *Clostridium difficile* infections in Veterans: role of vitamin D deficiency

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(*Accepted 1 December 2009; first published online 8 January 2010*)

SUMMARY

Clostridium difficile and staphylococcal infections are associated with increased morbidity, mortality and healthcare costs. Vitamin D deficiency may also contribute to increased healthcare costs. There is increasing evidence that vitamin D may have an antimicrobial role. We examined the relationship of serum 25(OH)D levels to staphylococcal and *C. difficile* infections to determine if vitamin D deficiency was associated with adverse outcomes. In the outpatient setting, vitamin D deficiency in patients with *C. difficile* and staphylococcal infections were associated with significantly increased total outpatients costs and fee-based consultation. Laboratory expenses had a trend towards higher costs in the vitamin D-deficient group but did not reach statistical significance. The differences were most clearly seen in the in-patient group with enhanced laboratory, pharmacy and radiology costs. These differences resulted in vitamin D-deficient patients with *C. difficile* or staphylococcal infections having costs more than five times higher than the non-deficient patients. The total length of hospital stay was four times greater in the vitamin D-deficient group. In addition, the total number of hospitalizations was also significantly greater in the vitamin D-deficient group. Surgery costs demonstrated a tendency to be higher in the vitamin D-deficient group but failed to reach statistical significance. Vitamin D deficiency is intimately linked to adverse health outcomes and costs in Veterans with staphylococcal and *C. difficile* infections in North East Tennessee. We recommend that vitamin D status be checked in patients with these infections and appropriate therapy be instituted to restore vitamin D level to normal in an expeditious manner.

Key words: *Clostridium difficile*, health costs, public health, *Staphylococcus aureus*, vitamin D deficiency.

INTRODUCTION

Vitamin D deficiency has reached pandemic proportions with significant impact on the induction and outcome of many chronic diseases [1]. The benefits of a vitamin D replete state remain poorly recognized [2]. In addition to the potential benefits of vitamin D on innate immunity there is increasing evidence for existence of an antimicrobial effect. Over 20 years ago, Feindt & Ströder [3] demonstrated by *in vitro* experiments that vitamin D3 proved lethal

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Table 1. *Sample characteristics: vitamin D status* (*deficient*/*non-deficient*)

	Full sample ($N=52$)	Deficient ($n=31$)	Non-deficient ($n=21$)
Age, yr, mean (range)	69·1 (41–92)	67·1 (41–88)	72·1 (53–92)
Gender (% male)	94·2	93·5	95·2
Race (% Caucasian)	94·2	93·5	95·2
State of residence (% Tennessee)	92·3	90·3	95·2
25(OH)D (ng/ml), mean (range)	25·0 (7–140)	13·8 (7–19·9)	36·5 (20–140)

Apart from 25(OH)D levels, none of the differences between the groups were statistically significant.

or markedly inhibited the growth of several bacterial strains including *Staphylococcus aureus*. Several studies have indicated a potential role for vitamin D in respiratory tract infections in both children and adults [4, 5]. Vitamin D receptor haplotypes may determine the susceptibility to HIV infection in intravenous drug abusers [6]. Moreover, antiviral and anti-tuberculous effects of vitamin D have also been described [7, 8].

Clostridium difficile is a growing problem in hospitals, especially among elderly patients [9], *C. difficile* infection is the most frequent cause of healthcare-associated infectious diarrhoea in industrialized countries [10, 11]. *C. difficile* has demonstrated progressive increase in virulence and is often refractory to treatment [12]. The increasing prevalence of the spread of *C. difficile* in the community, virulence and frequent relapse has created an urgent need to identify new effective treatments for this infection.

About one-third of the US population is colonized with *S. aureus* [13], and the rates of *S. aureus* bacteraemia are increasing [14]. *S. aureus* was the most common cause of nosocomial infections reported in the National Nosocomial Surveillance System between 1990 and 1996 [14, 15]. Staphylococcal infections were associated with high costs and large numbers of deaths in the New York City metropolitan area [15]. *S. aureus* has a profound impact on length of hospitalization and patient outcomes [13].

Given the economic burden of these two infections, we initiated a study to determine if vitamin D status was related to the healthcare outcomes and costs associated with infections with these two organisms.

METHODS

This study was conducted at James H. Quillen Veterans Medical Facility in the Southeastern United States. The Research and Development committee at VAMC and the institutional review board at the affiliated university approved the study. Data were obtained electronically through retrospective review after personal information was redacted. The sample included all patients diagnosed with either methicillin-sensitive *Staphylococcus aureus* (MSSA) or *C. difficile* infections from 2000 to 2008 that also had serum 25-hydroxyvitamin D [25(OH)D] analysis run within 3 months of the initial diagnosis. The 25(OH)D assay was done by immunochemiluminometric assay (Labcorp, USA). The costs were estimated by the technical guidelines via the Decision Support System and clinical National Data Extracts standardized by the VA as previously reported [16]. Costs in the year following diagnosis were broken down into separate in-patient and outpatient categories (i.e. laboratory, pharmacy, radiology, surgery, primary care, emergency room, etc.). For each of the cost categories, a total amount (US$) was analysed. Dichotomous service utilization variables were constructed to represent whether a patient had incurred that type of cost. No cost in a particular category meant that service was not used. Fees refer to costs incurred by the VA as a result of consultation and/or procedures performed in the private sector.

Utilizing diagnosis and procedure codes specified in the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) [17], the database was queried for patients with a discharge diagnosis code of 008·45 reflecting *C. difficile*/pseudomembranous colitis, patients with staphylococcal infections were identified using the ICD-9 code 041·11.

The final sample contained 52 patients, 29 with staphylococcal and 23 with *C. difficile* infections (see Table 1). There were no significant differences between patients with *S. aureus* and patients with *C. difficile* regarding their 25(OH)D level [24·6 *vs.*

https://doi.org/10.1017/S0950268809991543 Published online by Cambridge University Press

Table 2. *Costs incurred in staphylococcal and clostridial infections in relation to vitamin D status* ($N=52$)

	Vitamin D (ng/ml)		
Cost/care parameter	<20	>20	*P*
Outpatient			
Costs (US$)			
Primary care	664	446	0·18
Pharmacy	2105	1401	0·19
Laboratory	532	339	0·06
Radiology	449	408	0·39
Surgery	231	388	0·34
Emergency room	329	291	0·41
Fee-based	4169	477	0·05
Total outpatient	11 208	7246	0·05
Total number of clinic visits	19·3	13·7	0·12
In-patient			
Costs (US$)			
Pharmacy	5841	952	0·02
Laboratory	2136	346	0·01
Radiology	1340	191	0·00
Surgery	3121	396	0·06
Fee-based	2202	836	0·15
Total in-patient	36 576	6472	0·00
Total number of stays	1·8	1·1	0·03
Total number of in-patient days	18·9	4·1	0·00

25(OH)D <20 ng/ml deemed vitamin D deficient.

22·6; $t(50)=0·47$, $P=0·63$] or status [58·6% deficient *vs.* 60·9% deficient; $\chi^2(1)=0·03$, $P=0·87$]. Thus, remaining analyses were performed using the combined sample of 52 patients.

Statistical analysis

25(OH)D level was analysed both as a continuous and a dichotomous variable. Vitamin D deficiency was defined as a 25(OH)D level of <20 ng/ml [1]. Statistical analyses were performed using SPSS software, version 14.0 (SPSS Inc., USA). All variables were checked for outliers and normality of distribution before analyses were performed. Correlations and χ^2 analysis were used to examine the association between type of infection and 25(OH)D level and deficiency status. *t* tests were used to examine the associations between vitamin D status and the cost and service utilization variables.

RESULTS

In the outpatient setting, vitamin D deficiency in patients with *C. difficile* and staphylococcal infections were associated with significantly increased total outpatient costs and fee-based consultation (Table 2). Laboratory expenses had a trend towards higher costs in the vitamin D-deficient group but did not reach statistical significance.

As shown in Table 2, the differences between the two groups were most clearly seen in the in-patient group with enhanced laboratory, pharmacy and radiology costs. These differences resulted in vitamin D-deficient patients with *C. difficile*/staphylococcal infections having costs more than five times higher than the non-deficient patients. The total length of hospital stay was four times greater in the vitamin D-deficient group. In addition the total number of hospitalizations was also significantly greater in the vitamin D-deficient group. Surgery costs demonstrated a tendency to be higher in the vitamin D-deficient group but failed to reach statistical significance.

DISCUSSION

Our findings in a Veterans' population with *C. difficile* and staphylococcal infections indicate a link between vitamin D deficiency and adverse outcomes including increased healthcare utilization and expenses. This report is, to the best of our knowledge, the first to indicate that vitamin D deficiency may play an important role in limiting the success of traditional therapies in these two bacterial infections.

There is an increasing incidence of both *S. aureus* and *C. difficile* infections resulting in increased healthcare costs, morbidity and mortality. The traditional use of antibiotics has been implicated in the induction of superinfections with *S. aureus* and in some cases may play a more direct role in the induction of infections such as *C. difficile*. Given the prevalence of vitamin D deficiency in Veterans [16], we believe that vitamin D has an important antimicrobial role with the potential to offer substantial cost savings linked to hospitalization for *C. difficile* and staphylococcal infections.

The link between suboptimal vitamin D status and infections is not new. An association between bacterial vaginosis and maternal vitamin D deficiency has been reported in pregnant women [18]. In patients on regular haemodialysis, serum 25(OH)D levels were significantly correlated with serum *H. pylori*-specific IgG antibody titres even when adjusted for age and duration of dialysis [19]. In HIV-infected adults an inverse relationship between $1,25(OH)_2D$ (the active

https://doi.org/10.1017/S0950268809991543 Published online by Cambridge University Press

form of vitamin D) level and mortality and positive correlations between $1,25(OH)_2D$ levels and CD4+ cell counts have been observed [20].

Serum 25(OH)D levels were inversely associated with recent upper respiratory infections in the Third National Health and Nutrition Examination Survey [21]. In Indian children aged <5 years, subclinical vitamin D deficiency was a significant risk factor for severe acute lower respiratory tract infection [22]. There may be a dose-related effect since supplementation with 2000 IU of vitamin D in a study by Li-Ng and colleagues was not associated with decreased upper respiratory tract infections [23]. The levels reached following supplementation in that study were $\sim$35 ng/ml (88 nmol/l). These values are significantly below the values seen in humans exposed to liberal sunlight, in whom the values are $\sim$60 ng/ml. It may also be possible that factors other than serum vitamin D level play a role in susceptibility to infection. The vitamin D receptor is ubiquitous; however, genetic polymorphisms in the vitamin D receptor may also determine the risk of acquiring infections such as tuberculosis [24, 25].

Animal studies also lend support the antimicrobial effects of vitamin D. In an experimental model of turkey osteomyelitis, vitamin D treatment resulted in reduced bacterial presence in tissue and improved mortality [26]. In studies in mice, an overload of vitamin D had a protective effect against some strains of *Trypanosoma cruzi* infections [27].

The role of vitamin D as an antimicrobial agent acting through multiple mechanisms is becoming increasingly recognized. These mechanisms have been reviewed by Bikle [2] and indicate a potential boost in innate immunity by vitamin D. Gombart *et al*. [28] proposed that 1,25-dihydroxyvitamin D3 [1,25D(3)] induced expression of the human cathelicidin antimicrobial peptide (CAMP) gene. Their findings have since been confirmed by others [7] and indicate that vitamin D increases the body's production of naturally occurring antimicrobial peptides such as cathelicidin [7]. Cathelicidin is required for the 1,25D(3)-triggered antimicrobial activity against intracellular *Mycobacterium tuberculosis* [8]. Furthermore, Liu *et al*. [8] observed that sera from African-American individuals, known to have increased susceptibility to tuberculosis had low vitamin D levels and were inefficient in cathelicidin messenger RNA induction. Thus the link between vitamin D-mediated and toll-like receptor activation may also play a role in susceptibility to infections. In patients initiating chronic haemodialysis, low baseline levels of cathelicidin are independently associated with an increased risk of death attributable to infection [28].

The current recommendations for vitamin D intake while adequate for preventing rickets are clearly inadequate for optimal health. It is clear that much larger doses of vitamin D than previously surmised, e.g. a 300 000 IU bolus, can be used safely to treat vitamin D deficiency [29]. The potential to boost cathelicidin by short-term intensive high-dose vitamin D replacement and thereby influence infectious processes remains to be seen.

Our study does have certain inherent limitations. The current study involves Veterans and given its retrospective nature not all factors which could have influenced outcomes could be controlled. The strength of our study, similarly to previously published studies, comes from documentation of an important and unique association [30]. The present conclusions could also be explained by increased severity of illness in the vitamin D-deficient group. However, the mean serum levels of 25(OH)D found in the deficient group in our study are comparable to levels in elderly adults in winter [31] and 25(OH)D levels of <10 ng/ml have been reported in 35–50% of male university students living in Riyadh, Saudi Arabia [32]. As such, it is likely that vitamin D deficiency contributes to healthcare costs for these two bacterial infections rather than merely reflecting the degree of illness. Furthermore, our findings are consistent with the benefits of a vitamin D replete state to improve innate immunity in critically ill patients with sepsis [33]. Testing for vitamin D remains suboptimal and as such an adequate sample size in order to extend these observations to methicillin-resistant *S. aureus* was not possible. However, given the significance of our findings, we believe our conclusions should provide impetus to initiate additional studies to evaluate this important issue.

In conclusion, we believe that achieving a vitamin D replete state should be given high priority when treating *C. difficile* and staphylococcal infections, and possibly other infections. Studies by Ginde *et al*. [34] indicate that the prevalence of vitamin D deficiency has become more marked in recent years and as such appropriate replacement may offer immune and antimicrobial benefits at minimal cost. This benefit may be added to the long list of health benefits associated with adequate vitamin D reserves including improved well-being and enhanced longevity [35] with a projected significant savings in healthcare costs [36].

Moreover, the possible synergy with antibiotics by the therapeutic effects of a vitamin D-replete status remains an exciting avenue for further exploration.

ACKNOWLEDGEMENTS

We thank Nancy Milligan and the Mountain Home VAMC library staff and Johnson City Medical Center Library staff for their assistance. We appreciate the helpful comments by Felix Sarubbi, M.D. and Jonathan Moorman, M.D., Division of Infectious Diseases, ETSU and Dr Guha Krishnaswamy, Division of Allergy Immunology, ETSU.

DECLARATION OF INTEREST

None.

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