



L Ray Matthews^{1*}, Yusuf Ahmed², Omar Danner¹, Michael Williams¹, Carl Lokko¹, Jonathan Nguyen¹, Keren Bashan-Gilzenrat¹, Diane Dennis-Griggs¹, Nekelisha Prayor¹, Peter Rhee⁴, Ed W Childs¹, Kenneth Wilson³ and William B Grant⁵

¹Morehouse School of Medicine, Atlanta, GA, USA

²Sidra Medical and Research Center, Doha, Saudi Arabia

³Michigan State University College of Human Medicine, East Lansing, MI, USA

⁴Grady Memorial Hospital, Atlanta, GA, USA

⁵Sunlight, Nutrition and Health Research Center (SUNARC) San Francisco, CA, USA

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*Corresponding author: L Ray Matthews, Associate Professor of Surgery, Morehouse School of Medicine, Department of Surgery, 720 Westview Drive, SW, Atlanta, GA 30310, Tel: (404) 616-2391; Fax: (404) 616-1417; E-mail: lemattews@msm.edu; rmatt63@yahoo.com

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Research Article

Aggressive Treatment of Vitamin D Deficiency in Hispanic and African American Critically Injured Trauma Patients Reduces Health Care Disparities (Length of stay, Costs, and Mortality) in a Level I Trauma Center Surgical Intensive Care Unit

Abstract

Background: Socioeconomics only account for 18% of all healthcare disparities. Healthcare disparities in the intensive care unit (ICU) have been well documented and persist in spite of previous government and medical interventions. Vitamin D deficiency is the most common nutritional deficiency in the United States and the world. This deficiency has been largely overlooked in the debate on healthcare disparities.

Hypothesis: We hypothesize that low vitamin D levels (a steroid hormone that activates CD4, a T-cell for immune response) and a low CD4 cell count (a T-cell and a marker of a weak immune system) account for most of these healthcare disparities seen in Hispanic and African American patients. We further hypothesize that aggressive treatment of vitamin D deficiency decreases intensive care unit (ICU) length of stay (LOS), ICU cost, and mortality rate in this patient population.

Methods: We performed a prospective study of the vitamin D status on 316 Hispanic and African American patients admitted to Grady Hospital SICU from August 2009 to September 2011. The patients were divided into 3 groups: Group 1 was treated with vitamin D 50,000 international units (IU) weekly, orally or nasogastric tube (50,000-400,000 IU) for up to 8 weeks; Group 2 was treated with vitamin D 50,000 IU daily for 5 days (250,000 IU of vitamin D); and Group 3 patients (aggressive treatment) received vitamin D 50,000 IU daily down the nasogastric tube for 7 consecutive days. The injury severity score (ISS) was a mean of approximately 15 in all three groups. There wasn't any statistical difference between the three groups in terms of injury severity. A CD4 cell count was measured in a subset of 180 patients to evaluate as a marker for potential immune system compromise or weak immune system. In our surgical intensive care unit, Hispanic and African American patients had lower vitamin D levels and CD4 counts up to 40% lower than Caucasian Americans.

Results: The mean vitamin D levels for the three groups were as follows: Group 1, 10.22±0.60 ng/ml; Group 2, 13.78±0.72 ng/ml; and Group 3, 15.89±0.87 ng/ml (normal ≥ 40 ng/ml). Mean ICU LOS decreased with aggressive treatment of vitamin D deficiency from 13.21±2.04 days in Group 1 to 11.53±2.45 days in Group 2 to 6.3±0.79 days in Group 3 (p-value, 0.021). Mean ICU cost also decreased with aggressive treatment of vitamin D deficiency by the following: Group 1, \$50,934.25±7,877; Group 2, \$44,464.50±9,458.50; and Group 3, \$24,433.02±2,887.75 (p-value, 0.021). Mortality rate decreased from 11.0% in Group 1 to 9.4% in Group 2 to 6.4% in Group 3 (p-value, 0.486). This trend shows a clinically significant 42% reduction in mortality rate which is clinically significant even though it is not statistically significant.

Conclusion: We conclude that a compromised immune state due to low vitamin D status and low CD4 cell count may explain a large percentage of healthcare disparities. Aggressively optimizing serum vitamin D status to ≥ 40 ng/ml may be the one of the most important steps in solving healthcare disparities in the United States. Further studies on low vitamin D levels/low CD4 counts are needed to fully address healthcare disparities.

Introduction

Healthcare disparities have been well documented in the United States and persist despite previous medical and government interventions. The root cause of these disparities remains unclear and has eluded medical researchers for decades. It is recognized by many authorities that multiple factors contribute to healthcare disparities in the United States, such as socioeconomic (education and employment), lifestyle behaviors (physical activity, alcohol, and drug use), and access to healthcare services [1]. However, several studies have shown that these factors do not provide adequate rationale for the observed disparities. In fact, the influence of all these factors is modest and explains less than 20% of healthcare disparities [2]. Furthermore, recent reports have concluded that progress in eliminating these differences in healthcare outcomes between Caucasian Americans (CAs) and non-Caucasians remains bleak, and efforts to date have had a negligible impact on resolving this challenge.

It has become increasingly well-recognized that significant health disparities exist between AAs and CAs. According to data released by the Centers for Disease Control and Prevention, and other governmental agencies, African Americans (AA) and Hispanic Americans (HA) tend to have higher disease rates and mortality rates than Caucasian Americans (CA) [3]. Many studies are beginning to surface that suggest dietary differences are major contributors to some of these health disparities. However, which nutritional deficiencies represent the greatest risk remains a subject of intense research and debate.

Vitamin D deficiency is rampant throughout our society and is the most common nutritional deficiency in the United States population affecting over 70% of the population [4]. Common causes of vitamin-D deficiency include: poor vitamin-D content in foods (very few foods are fortified with vitamin-D); sunscreen use which blocks 95% of vitamin-D production by the skin; and melanin pigment in dark-skinned people (African-American) who need 3x's-6x's longer sun exposure than Caucasians to produce the same amount of vitamin-D. This is because melanin serves as a natural sun screen blocking 98% of vitamin D production in dark -skinned people. Thus, the average AA/HA tend to have vitamin D levels up to 43% lower than the average WA. Other plausible causes of this vitamin D deficiency include in the elderly, aging skin which reduces vitamin-D production by 70% at age 70; obesity which causes vitamin-D to be stored in the fat cells instead of the liver in normal sized people; chronic kidney disease; lack of, or inadequate vitamin-D supplementation (current RDA too low for optimal health); and seasonal variations, latitude, and time of day [4-11]. In addition, people living above the 32nd latitude (e.g., Atlanta, Georgia) do produce vitamin-D from November - March. This is because the sunlight hits the northern hemisphere at a 45° angle, instead of the 90° angle required to produce ultraviolet band of wavelengths from 290-315 nm, which is essential for vitamin-D production in the skin from 10 am until 3 pm [4].

Humans get vitamin D from their diet, exposure to sunlight, and from dietary supplements [12]. Solar ultraviolet B radiation

(wavelength, 290-315 nm) penetrates the skin to convert cholesterol to vitamin D₃ [13]. Very few foods are fortified with vitamin D. Thus, limited sun exposure (15 minutes) and supplements are necessary to reach their maximal requirements [14].

We hypothesize that low vitamin D levels and a low CD4 cell count (a marker of a weak immune system) account for a large percentage of these healthcare disparities. We further hypothesize that aggressive treatment of vitamin D deficiency decreases intensive care unit (ICU) length of stay (LOS), ICU cost, and mortality rate.

Methods

Setting: Grady Memorial is a Level I trauma center located in Atlanta, Georgia with over 3,200 trauma admissions per year. Blunt trauma accounts for 70% of the admissions and penetrating trauma accounts for 30% of the admissions.

We conducted a prospective study on the vitamin D status on 316 Hispanic and African American patients admitted to Grady Hospital from August 2009 to September 2011. Vitamin D levels were measured by high pressure liquid chromatography (HPLC) and tandem mass spectrometry at Quest Lab. We defined vitamin D deficiency as a level ≤ 40 ng/ml. A CD4 cell count was measured in a subset of 180 patients to evaluate as a marker for potential immune compromise or a weak immune response system.

The injury severity score (ISS) was a mean of approximately 15 in all three groups. There wasn't any clinically significant difference between the 3 groups in terms of severity of injury. Blunt trauma accounted for 70% of the injuries in all three groups. Penetrating trauma accounted for 30% in all groups.

This research was approved by Morehouse School of Medicine Institution Review Board. The patients were divided into 3 groups: Group 1 was treated with vitamin D 50,000 IU weekly, orally/nasogastric tube for up to 8 weeks or discharge for SICU (50,000-400,000 IUs of vitamin D); Group 2 was treated with vitamin D 50,000 IU orally or down their nasogastric tube daily for 5 days (250,000 IU of Vitamin D); and Group 3 (aggressive treatment) was treated with vitamin D 50,000 IU daily for 7 straight days (350,000 IU of vitamin D) we examined patient's baseline demographics which include the following: age, race, gender, and baseline biochemical markers such as vitamin B12 levels, albumin, pre-albumin, and calcium. To examine the potential impact of comorbidities, we evaluated the patients for cardiovascular disease, pneumonia, urinary tract infections, pulmonary embolus, and trauma injuries.

Our primary outcomes assessed in this study were ICU LOS and ICU cost. Secondary outcome studied was mortality rate. Statistical analysis was conducted using SPSS 16.0 software (SPSS, Chicago, Illinois). Data was summarized as means plus or minus standard deviation and proportion (percentages) for continuous and qualitative data, respectively. A p-value < 0.05 was considered statistically significant.

Exclusion criteria

Patients admitted to the SICU for less than 24 hours were excluded from the study. Vitamin D levels were drawn on all patients upon admissions to the SICU.

Results

The serum vitamin D status of 316 Hispanic (10.5%) and African American (89.5%) patients were measured. The baseline characteristics such as age, race, and gender are presented in table 1. The mean vitamin D levels for the 3 treatment groups were as follows (Table 2), Group 1 was 10.22±0.60 ng/ml; Group 2 was 13.78±0.72 ng/ml; and Group 3 was 15.89±0.87 ng/ml (p= 0.001) Figure 1. The mean ICU LOS for the three groups was 13.21±2.04 days for Group 1, 11.53±2.45 days for Group 2, and 6.3±0.79 days for Group 3 (p- value 0.021) Figure 2. The mean ICU cost for the three treatment groups was \$50,934.25±7.877.60 for Group 1, \$44,464.50±9,458.50 for Group 2, and \$24,433.02±2,887.75 for Group 3. (P= 0.021).

The mortality rate is Group 1 was 11.0% versus 9.4% for Group 2 versus 6.4% for Group 3. (p= 0.486). A 14.6% mortality relative risk reduction in group 2, compared to group 1, and 42.1% reduction in mortality risk in Group 3 when compared to Group 1, even though this not statistically significant, we think that, this mortality relative risk reduction is clinically significant Figure 3.

We also measured a subset of CD4 cell count in 180 patients in Group 2 and Group 3. Optimal functioning of the immune system requires optimal vitamin D levels to activate or “to arm” the T-cells (CD4). A low CD4 cell count (plus a low vitamin D level) would give us a snapshot of a “compromised immune system” in our patient population which would partially explain worse outcomes. This predispose these patients to more aggressive and less responsive sepsis/infections, myocardial infarction, strokes, and other chronic diseases of aging in the surgical intensive care unit.

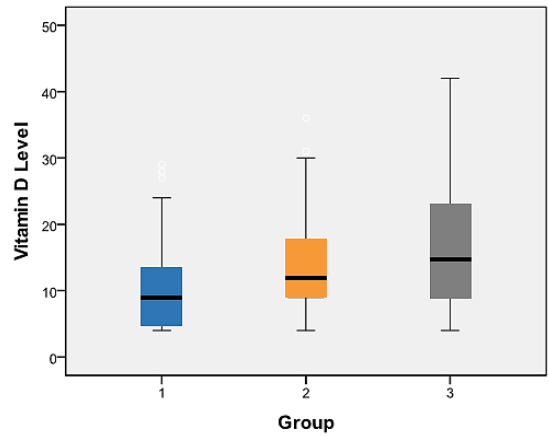


Figure 1: Mean Vitamin D Level for the Groups.

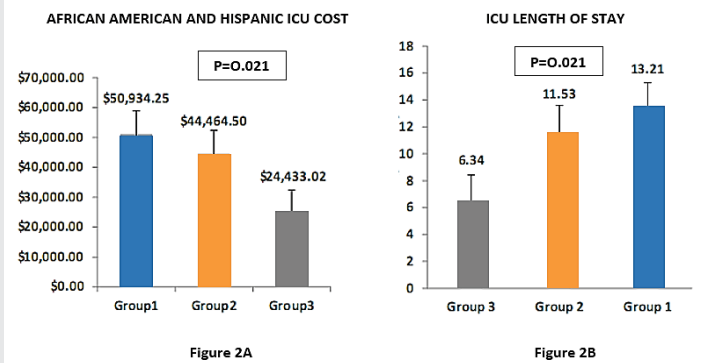


Figure 2: (Fig. 2a) Shows the Icu Treatment Cost; (Fig. 2b) - Shows the Icu Length of Stay

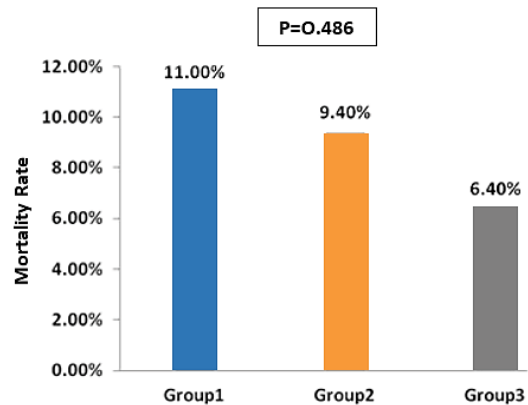


Figure 3: Groups Mortality Rate.

Table 1: Groups Characteristics.

CHARACTER	GROUP 1 N (%)	GROUP 2 N (%)	GROUP 3 N (%)
MALE	69(62.7%)	75(78.1%)	80(72.7%)
FEMALE	41(37.3%)	21(21.9%)	30(27.3%)
AFRICAN-AMERICAN	101(91.8%)	82(85.5%)	100(90.9%)
HISPANIC	9(8.2%)	14(14.6%)	10(9.1%)

Table 2: Groups Comparison.

VARIABLE	GROUP 1		GROUP 2		GROUP 3	
	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
AGE	110	47.86±19.38	96	38.77±16.20	110	41.31±17.20
VITD_LEVEL	110	10.22±6.23	88	13.78±6.81	94	15.89±8.43
ICU_LOS	110	13.21±21.42	96	11.53±24.03	110	6.34±7.85
ICU_COST	110	50934.25±7878.0	37	44464.50±9458.51	110	24433.02±2887.75
CD4_LEVEL	***	*****	29	422.57±49.10	94	554.04±310.70

*****= variable was not measured.

The mean CD4 cell count for patients in Group 2 was 422.57±49.1 cells per cubic milliliter (ml) of blood (normal is 500 -1500 cells per cubic ml of blood). The mean CD4 cell count in Group 3 was 554.04±32.05 (p= 0.029) Figure 4, also there is positive correlation between vitamin D treatment and the increase of the CD4 (r=0.175, p=0.045). Further studies are needed to evaluate if there is a direct correlation between low vitamin D levels and low CD cell counts; however, vitamin D is a very strong immune modulator Figure 5.

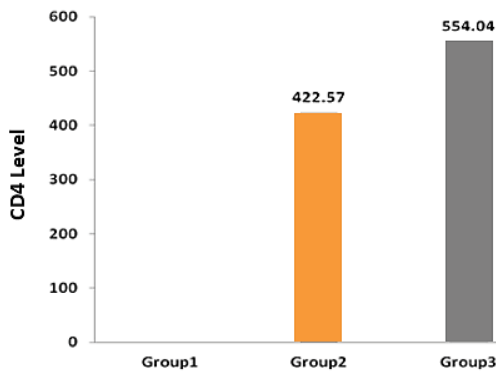


Figure 4: Cd4 Levels in Groups 2 and 3 -- The Group 1 Cd4 Levels were not measured.

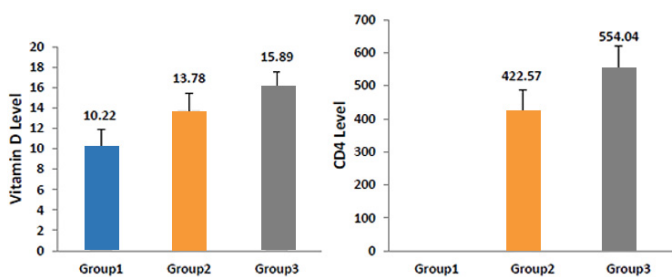


Figure 5: Shows the increase of the vitamin d is correlated with cd4 increase.

Discussion

Why is vitamin D important to our general and overall health? Vitamin D is a pleiotropic seco-steroid hormone with effects throughout the body. It is hydroxylated at the 1 and 25 position to produce activated vitamin D. Vitamin D receptors have been identified on nearly all cells and tissues in the human body [4]. As Vitamin D is actually a steroid hormone, it works on the DNA in the nucleus of the cell on Vitamin D response-elements and thereby controls the expression of over 3,000 genes in the human body, including immune modulation (T-cell count and function) and inflammation (CRP, IL6, TNF, antimicrobial peptide, and free radical formation) [4,6,7].

Several studies reported that vitamin D deficiency has important health consequences due to its influence on immune function and other organ systems have begun to surface [15]. Consequently, many chronic diseases such as cardiovascular diseases (congestive heart failure, coronary artery disease, and myocardial infarctions), strokes, osteoporosis, rickets, osteopenia, rheumatoid arthritis, muscle cramps, muscle pain, joint pain, cancers (17 different types), autoimmune diseases, flu, colds, depression, type 2 diabetes, muscle weakness, and falls in elderly patients have been strongly associated with vitamin D deficiency [4,6,7].

A meta-analysis of 18 randomized clinical trials on vitamin-D supplementation found that randomization to vitamin-D was associated with lower, all-cause mortality rates

in the general population [8]. Although it is well known that the combination of vitamin-D and calcium is necessary to maintain bone density as people age [16], vitamin-D deficiency may also be an independent risk factor for falls and fractures among the elderly [17]. Another study showed that vitamin-D levels less than 17.8 ng/ml increase the risk of death 26% from all causes in the general population [8-10].

In fact, higher serum levels of 25-hydroxyvitamin D (25[OH]D) have been shown to be associated with improved health outcomes [18,19]. Based on recent meta-analyses of several observations studies of differences in serum 25(OH)D levels for AAs versus CAs, lower vitamin D level may help to explain many of the health disparities that we have observed in America, and throughout the western society. The impact of suboptimal levels of 25(OH)D on proper immune function has been elucidated by several recent investigations. As a result of lower vitamin D levels in AA/HA, there tends to be a trend towards a less responsive immune system, increased inflammation, increased oxidative stress (oxygen free radical formation), and increased endothelial dysfunction in these patient populations, which may explain most of the present healthcare disparities and chronic diseases [11].

In our previous study, we demonstrated that vitamin D deficiency was associated with increased mortality rates and length of stay in critically ill hospitalized patients admitted to the surgical intensive care unit. However, the question is what is the mechanism by which vitamin D deficiency actually causes compromise of immune function? And are there other identifiable markers which shed more light on the correlation between vitamin D deficiency and poorer health outcomes in the critical care setting? We postulate that vitamin D deficiency is associated with decrease CD4+ T-lymphocyte counts, which decreases adaptive immunity and worsens the ability of the host to overcome infectious and pro-inflammatory insults, such as, sepsis, multiple organ failure syndrome (MOFS) and adult respiratory distress syndrome (ARDS).

Limitations in our study include the loss of outpatient follow up with many of our patients once discharged from the hospital. Many patients followed up with their local medical physician or failed to keep their appointments. Also, we did not take into account the seasonal variations of vitamin D levels which are 20-30% lower in the winter months due to decreased vitamin D production.

Any discussion on healthcare reform should address correcting the most common nutritional deficiency in the United States and the world. Vitamin deficiency is associated with nearly all of the chronic diseases that drive up healthcare costs. Normalizing everybody's serum vitamin D level ≥ 40 ng/ml could potentially reduce healthcare costs by \$ 400 billion per year [20]. We are presently spending \$ 3.0 trillion on healthcare annually. We have demonstrated in this study that higher vitamin D levels reduce hospital costs and mortality [21-29].

Conclusion

We conclude that a compromised immune system due to a low vitamin D status and a low CD4 cell count may explain a large percentage of healthcare disparities. Aggressive optimizing serum vitamin D status to > 40 ng/ml may be one of the most important steps in treating healthcare disparities in the United States. Further investigation into these very important biologic factors (low vitamin D levels and low CD4 cell counts) is needed to more clearly delineate these findings.

References

- Grant WB, Peiris AN (2010) Possible role of serum 25-hydroxyvitamin D in black-white health disparities in the United States. *J Am Med Dir Assoc* 11: 617-628. [Link: https://goo.gl/cRcKh9](https://goo.gl/cRcKh9)
- Peebles L (2010) Unexplained differences in hospital death rates. *Reuter's health* 22. [Link: https://goo.gl/37u4Kz](https://goo.gl/37u4Kz)
- Fiscella K, Franks P (2010) Vitamin D, race, and cardiovascular mortality: findings from a national US sample. *Ann Fam Med* 8: 11-18. [Link: https://goo.gl/iC8IG0](https://goo.gl/iC8IG0)
- Holick MF (2007) Vitamin D deficiency. *N Engl J Med* 359: 266-281. [Link: https://goo.gl/ljYJRZ](https://goo.gl/ljYJRZ)
- Ginde AA, Liu MC, Camargo CA (2009) Demographic differences and trends of vitamin D insufficiency in the general population, 1998-2004. *Arch Intern Med* 169: 626-632. [Link: https://goo.gl/kFmqbv](https://goo.gl/kFmqbv)
- Holick MF (2006) High prevalence of vitamin D inadequacy and implications for health. *Mayo Clin Proc* 81: 353-373. [Link: https://goo.gl/L83gJ3](https://goo.gl/L83gJ3)
- Adams JS, Liu PT, Chun R, Modlin RL, Hewison M (2007) Vitamin D in Defense of the Human Immune Response. *Ann N Y Acad Sci* 1117: 94-105. [Link: https://goo.gl/j36mhx](https://goo.gl/j36mhx)
- Lee P, Eisman JA, Center JR (2009) Vitamin D deficiency in critically ill patients. *N Engl J Med* 360: 1912-1914. [Link: https://goo.gl/b8vwzz](https://goo.gl/b8vwzz)
- Dobnig H, Pilz S, Scharnagl H, Renner W, Seelhorst U, et al. (2008) Independent association of low serum 25-hydroxyvitamin d and 1,25-dihydroxyvitamin D levels with all-cause and cardiovascular mortality. *Arch Intern Med* 168: 1340-1349. [Link: https://goo.gl/a7inWW](https://goo.gl/a7inWW)
- Melamed ML, Michos ED, Post W, Astor B (2010) 25-hydroxyl vitamin D levels and the risk of mortality in the general population, *Arch Intern Med* 168: 1629-1637. [Link: https://goo.gl/rc8wpd](https://goo.gl/rc8wpd)
- Grant WB, Peiris AN (2010) Possible role of serum 25-hydroxyvitamin D in black-white health disparities in the United States. *J Am Med Dir Assoc* 11: 617-628. [Link: https://goo.gl/l40x0U](https://goo.gl/l40x0U)
- DeLuca HF (2004) Overview of general physiologic features and functions of vitamin D. *Am J Clin Nutr* 80: 1689S-1696S. [Link: https://goo.gl/Mfx6Sx](https://goo.gl/Mfx6Sx)
- Holick MF (2006) Resurrection of vitamin d deficiency and rickets. *J Clin Invest* 116: 2062-2072. [Link: https://goo.gl/lDdfQr](https://goo.gl/lDdfQr)
- Viet R (2004) Why the optimal requirements for vitamin D3 is probably much higher than what is officially recommended for adults. *J Steroid Biochem Mol Biol* 89-90: 575-579. [Link: https://goo.gl/1AYbF9](https://goo.gl/1AYbF9)
- Cantorna MT, Zhu Y, Froicu M, Wittke A (2004) Vitamin D status, 1,25-dihydroxyvitamin D3, and the immune system. *Am J Clin Nutr* 80: 1717S-1720S. [Link: https://goo.gl/qSyGVm](https://goo.gl/qSyGVm)
- Dawson-Hughes B, Harris SS, Krall EA, Dallal GE (1997) Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Engl J Med* 337: 670-676. [Link: https://goo.gl/7b1SCQ](https://goo.gl/7b1SCQ)
- Broe KE, Chen TC, Weinberg J, Bischoff-Ferrari HA, Holick MF, et al. (2007) A higher dose of vitamin D reduces the risk of falls in nursing home residents: a randomized, multiple-dose study. *J Am Geriatr Soc* 55: 234-239. [Link: https://goo.gl/js1uWa](https://goo.gl/js1uWa)
- Holick MF (2006) High prevalence of vitamin D inadequacy and implications for health. *Mayo Clin Proc* 81: 353-373. [Link: https://goo.gl/aarJ5b](https://goo.gl/aarJ5b)
- Bischoff-Ferrari HA, Giovanannucci E, Willett WC, Dietrich T, Dawson-Hughes B (2006) Estimation of optimal serum concentrations of 25-hydroxyvitamin d for multiple health outcomes. *Am J Clin Nutr* 84: 18-28. [Link: https://goo.gl/YzNAFJ](https://goo.gl/YzNAFJ)
- Grant WB, Cross HS, Garland CF, Gorham ED, Moan J, et al. (2009) Estimated benefit of increased vitamin D status in reducing the economic burden of disease in Western Europe. *Prog Biophys Mol Biol* 99: 104-113. [Link: https://goo.gl/C1R8Hx](https://goo.gl/C1R8Hx)
- Matthews LR, Ahmed Y, Wilson KL, Griggs DD, Danner OK (2012) Worsening Severity of Vitamin D Deficiency is Associated with Increased Length of Stay, Surgical Intensive Care Unit Cost, and Mortality Rate in Surgical Intensive Care Unit Patients. *The American Journal of Surgery*. 204: 37-43. [Link: https://goo.gl/VjmXit](https://goo.gl/VjmXit)
- Matthews LR (2015) Daily High Dose Vitamin D Supplementation Reduces the Incidence of Myocardial Infarctions in Surgical Intensive Care Unit Patients. *J Clin Exp Cardiol* 6: 10. [Link: https://goo.gl/dmc4OW](https://goo.gl/dmc4OW)
- Matthews LR, Ahmed Y, Danner O, Moore C, Lokko C, et al. (2017) High Dose Vitamin D, Digoxin, and BiDil Reverse Congestive Heart Failure in a Critically ILL Trauma Patient and a Severely Obese Male Patient. *Glob J Medical Clin Case Rep* 4: 031-034. [Link: https://goo.gl/zJs67t](https://goo.gl/zJs67t)
- Matthews LR, Ahmed Y, Danner OK, Kwaysi G, Dennis-Griggs D, et al. (2017) Vitamin D, Glutamine, Evidence-Based Medicine, and Close Staff Supervision Reduce Mortality Rate at a Level I Trauma Center. *Glob J Medical Clin Case Rep* 4: 020-02. [Link: https://goo.gl/P2IVNm](https://goo.gl/P2IVNm)
- Matthews LR, Ahmed Y, Bashan-Gilzenrat K, Nguyen J, Okonkwo A, et al. (2016) A Short Essay: High Dose Vitamin D Supplementation Reduces Medical Malpractice Lawsuits in Critically ILL Trauma Patients. *Medical Research Archives* 4. [Link: https://goo.gl/JmaKvN](https://goo.gl/JmaKvN)
- Danner OK, Matthews LR, Francis S, Rao VN, Harvey C, et al. (2016) Vitamin D3 Suppresses Class II Invariant Chain Peptides Expression on Activated B Lymphocytes: A Plausible Mechanism for Down-Regulation of Acute Inflammatory Conditions. *J Nutr Metab* 2016: 8. [Link: https://goo.gl/UPDWvJ](https://goo.gl/UPDWvJ)
- Matthews LR, Gustafson C (2015) Enhanced Surgical Outcomes and Boosted Soft-tissue Wellness from Vitamin D Supplementation. *Altern Ther Health Med* 21: 68-72. [Link: https://goo.gl/oE3nYD](https://goo.gl/oE3nYD)
- Matthews LR, Danner OK, Ahmed Y, Dennis-Griggs DM, Frederick A, et al. (2012) Combination Therapy with Vitamin D3, Progesterone, Omega 3-Fatty Acids, and Glutamine Reverses Coma and Improves Clinical Outcomes in Patients with Severe Traumatic Brain Injuries: A Case Series of Three Patients. *International Journal of Case Reports and Images*. 4: 143-149. [Link: https://goo.gl/aKhp6l](https://goo.gl/aKhp6l)
- Matthews LR, Ahmed Y, Thomas C, Wilson K, Diane DG, et al. Economic Impact of Vitamin D Levels Less Than 18 ng/ml on Hospitals and Third Party Payers. *Critical Care Medicine* 43: 327. [Link: https://goo.gl/CKk0Ci](https://goo.gl/CKk0Ci)

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