TESTOSTERONE AND VITAMIN D CONCENTRATIONS IN MILITARY PERSONNEL FOLLOWING TRAUMATIC BRAIN INJURY

A Thesis
by
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Abstract

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Traumatic Brain injury (TBI) contributes to a large portion of injuries sustained by service members and can cause neuroendocrine dysfunction by damaging the pituitary or hypothalamus during injury. Hypopituitarism with gonadotropin deficiency is one of the most prevalent types of neuroendocrine dysfunction following TBI and has been predicted to cause long-term secondary hypogonadism in up to 16% of individuals with a TBI diagnosis. Although it's a different mechanism from neuroendocrine disorders, vitamin D deficiency may be associated with TBI sequelae. A few civilian studies have investigated vitamin D status post-TBI and high rates of vitamin D deficiency were prevalent. It is unclear if TBI causes low vitamin D, but if vitamin D is low prior to TBI it may exacerbate injury. The purpose of this study was to investigate testosterone and vitamin D status in active duty and retired service members, with and without a history of traumatic brain injury, and the frequency of testosterone replacement therapy prescriptions to identify targets for therapeutic treatments to improve long-term recovery. This retrospective de-identified medical review analyzed hormone assessments ordered for 4,285 active duty and veteran military personnel

at Womack Army Medical Center, Fort Bragg, NC from 2016-2018. Overall, 343 (8%) of service members had a medically diagnosed TBI. In all men, 19% were deficient in testosterone (< 270 ng/dl), and 10% had a testosterone prescription. Active duty men with history of TBI had lower testosterone compared to active duty men with no documented head injury (431 ± 162 vs 452 ± 170 ng/dl, p = 0.04), but there was no significant difference in veteran men. More than one-third (38%) of all service members were insufficient in vitamin D (< 30 ng/ml). Service members with a history of TBI had slightly higher vitamin D concentrations compared to those with no prior head injury, but the difference was minimal (2 ng/ml) and of little clinical significance. Overall there was a weak positive correlation between testosterone and vitamin D concentrations in men but not in women. Although our 8% diagnosis rate of TBI was lower than previous studies, we found slightly lower testosterone concentrations in active duty men with documented TBI. Correlations between testosterone and vitamin D concentrations were weak. However, our overall dataset shows a high prevalence of vitamin D insufficiency in both active duty and retired service members independent of TBI, further supporting that vitamin D status should be assessed regularly in service members.

Acknowledgments

I would like to recognize the Womack Army Medical Center Information Management Division and Dr. Cristóbal S Berry-Cabán for the data acquisition that made this research possible. I wish to express my deepest gratitude to my supervisor Dr. Laurel Wentz for guiding me through the research process and being an incredible mentor. I would also like to thank my committee member Dr. Roy Manan for the hours of statistical analyses she completed for this research and for all of her contributions to this thesis. Further appreciation goes to my committee member Dr. Melissa Gutschall for all that she does as the wonderful director of our graduate program and for her time spent editing all the drafts for this project. I especially appreciate my mother, brother and sister-in-law. Jackie, Bradley, and Megan, thank you for listening to me talk about this thesis for 2 years straight, supporting me in all of my dreams, and for reading all of the final drafts I was so proud of. Thank you to my boyfriend, Stephen, who encouraged me to complete a thesis when I was scared to pursue one and for always believing in me. Lastly, I am grateful for my Aunt Joanne, who has shown me support both emotionally and professionally.

Dedication

To my mom and dad for always helping me make my dreams come true, no matter how crazy they are.

Jacqueline, I am so grateful that you are my mother and I aspire to be like you. Your resilience in life and unconditional love to your family have shaped me into the person I am today. Thank you for being my best friend.

To my hero, Dr. Kenyon F. Tillotson, who will forever be alive in my heart. He was the most optimistic, loving and inspiring person I had ever known. I am truly blessed to have had such a caring, happy, innovative, and clever father. Considering his service in the Marines, his passion for education, and his notorious saying of "take your vitamin D!" when we didn't feel well, it goes without saying he would have loved to have read my thesis. Thank you for showing me that there is always a rainbow after the rain, I love you.

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Foreword

Chapter 2 of this thesis will be submitted to *The Journal of Military and Veterans' Health*, a peer-reviewed journal published by the Australasian Military Medicine Association and overseen by the JMVH Editorial Board; it has been formatted according to the style guide for that journal.

Chapter 1: Introduction

Problem

Traumatic brain injury (TBI) causes long-term consequences including degenerative diseases, psychiatric disorders and cognitive, behavioral, and physical defects that may prevent military personnel from performing to their greatest potential and negatively impact long-term health.[1,2] Since 2000, 413,858 service members have been diagnosed with at least one TBI, 83% of which were classified as mild TBI (mTBI).[3] Neuroendocrine dysfunction is a common consequence of TBI, as nearly half of all cases result in symptoms of neuroendocrine dysfunction.[4] Neuroendocrine dysfunction is the term for a variety of hormone imbalances directly related to the hypothalamus, pituitary and their axes and is characterized by fatigue, anxiety, irritability, depression, insomnia, infertility, cognitive deficits, and weight changes.[5,6] Pituitary dysfunction or hypopituitarism, is a biochemical deficiency in one or more endocrine axes by either an inadequate supply of hypothalamic-releasing hormones or the gland's inability to produce hormones.[7] Hypopituitarism with gonadotropin deficiency is one of the most prevalent types of neuroendocrine dysfunction following TBI and has been predicted to cause long-term secondary hypogonadism in up to 16% of individuals with a TBI diagnosis.[8,9] Secondary hypogonadism is caused by damage to the hypothalamic-pituitary-gonadal axis and is characterized by low testosterone with low to normal follicle stimulating hormone and luteinizing hormone levels in men.[10]

Although it's a different mechanism from neuroendocrine disorders, vitamin D deficiency may be associated with TBI sequelae. Vitamin D is a secosteroid hormone that regulates the expression of over 1000 genes with the vitamin D receptor (VDR).[11] Five studies have found vitamin D deficiency to be prevalent in patients following a TBI.[12-16]

However, numerous studies have shown high rates of vitamin D deficiency and insufficiency in military personnel and recruits overall.[17-23] Wentz et al.[23] found that 56% of service members who had vitamin D assessed at Womack Army Medical Center, Fort Bragg, NC to be deficient or insufficient in vitamin D (25-hydroxyvitamin D < 30 ng/ml). Thus, it remains unclear if low vitamin D exacerbates injury or TBI causes low vitamin D.[23]

TBI contributes to a large portion of injuries sustained by service members and may cause lasting effects such as sleep disorders, memory deficits, impaired judgment, aggression, and impulsivity.[6] TBI, neuroendocrine dysfunction, and vitamin D deficiency have many overlapping symptoms, making it difficult to distinguish hormonal abnormalities from post-concussive symptoms.[6,14] Post-concussive symptoms that parallel neuroendocrine dysfunction symptoms include fatigue, poor memory, anxiety, emotional lability, depression, weight gain or loss, and attention and concentration problems.[6] Low vitamin D status has been correlated with impaired cognitive function and depressive symptoms.[14]

Scientific Rationale

TBI has been shown to cause pituitary dysfunction, which manifests in low testosterone, and may have an effect on vitamin D status.[4,14] Pituitary dysfunction is caused by direct mechanical trauma, posttraumatic hypoxia, or shearing axonal injury to the central nervous system mechanisms of the hypothalamic-pituitary-target organ axes.[8,24] This injury affects hormone concentrations from either an inadequate supply of hypothalamic-releasing hormones or the gland's inability to produce hormones.[7] Testosterone production may be reduced post-TBI as a result of inflammatory cascade cytokines suppressing Leydig cell function in the testes, which in turn leads to hypothalamic-pituitary-gonadal axis dysfunction and suppresses testosterone.[24] Although controversial, the Endocrine Society recommends

testosterone replacement therapy for men with consistent symptoms and signs of androgen deficiency with low serum testosterone concentrations.[25] One study has investigated the effects of testosterone therapy after TBI but results have not been published to date.[26] However, androgen prescriptions recorded in military facilities increased from 19,494 in 2007 to 45,270 in 2011.[27] In 2017, 4.7 per 1,000 active service men underwent testosterone replacement therapy.[28]

Some evidence establishes an association between testosterone and vitamin D concentrations. For example, Nimptsch et al.[29] found that testosterone was positively correlated with vitamin D concentrations in older civilian men, possibly due to the expression of the vitamin D receptor and metabolizing enzymes in the Leydig cells of the testes. These data suggest that vitamin D has a supporting role in regulating testosterone production.[30] Furthermore, vitamin D may be important for attenuating inflammation post-injury, as several animal studies have shown neuroinflammation and cell death reduction and improved memory when vitamin D is added to progesterone treatments after TBI.[31-35] There are a few mechanisms to explain low vitamin D status following TBI. The vitamin D receptor (VDR) is located in neuronal and glial cells in the brain, suggesting vitamin D may be a possible neurosteroid through autocrine and paracrine function.[11] If vitamin D is in fact a neurosteroid, then it can modulate neuronal excitability and become a therapeutic approach for TBI outcomes.[36] Vitamin D's neuroprotective role following TBI has been explored in several studies, most of which have used animal models. Cui et al.[31] found vitamin D to be neuroprotective by its regulation of cell death following TBI in rats. Cekic et al.[37] suggested that vitamin D deficiency could exacerbate brain inflammation from TBI and hinder the effectiveness of progesterone treatment. Cekic & Stein[38] found increased inflammation after

TBI in vitamin D deficient rats and suggested that vitamin D deficiency produces a higher baseline level of inflammation, increased immune-inflammatory response, and a more severe secondary injury progression after TBI. Lee et al.[15] found vitamin D supplementation increased long-term performance and cognitive outcomes in mild-to-moderate vitamin D deficient patients, while another study found patients with vitamin D deficiency on admission to the neurological critical care unit had worse 3-month Glasgow Outcome Scores than vitamin sufficient patients.[32] Another mechanism contributing to reduced vitamin D in TBI patients is reduced sun exposure due to hospitalization, time off work, and depression.[16]

Significance

Numerous studies have shown a decrease in testosterone and vitamin D concentrations following TBI in civilians.[12-16,39-45] These studies have investigated mild, moderate, and severe TBI in relation to hypopituitarism and testosterone concentrations. Studies have shown severe hypopituitarism in all severities of TBI with hypogonadism being common. However, low testosterone results have varied based on injury severity.[9] Four studies have investigated testosterone status in military personnel following mild, moderate, and severe blast related TBI. These studies found low testosterone with injury with one study observed a significant decrease in testosterone 3 years after injury compared to controls.[4,46-48] These studies did not measure vitamin D status in those with TBI or altered testosterone or investigated rates of testosterone replacement therapy after TBI. Furthermore, studies investigating both male and female as well as active duty and veteran service members together are lacking. Five studies to date have investigated vitamin D status post-TBI. Jamall et al.[14] focused on moderate to severe TBI, while other studies have investigated mild, moderate, and severe TBI.[12,13,15,16] Jamall et al.[14] found nearly half of their patients

were deficient in vitamin D after all severities of TBI, while Toman et al.[16] found the lowest vitamin D concentrations in the most severe cases of TBI. Lee et al.[15] found 95% of patients were vitamin D deficient after TBI, showing that patients with mild-to-moderate TBI and inadequate vitamin D status who received vitamin D supplementation showed a greater degree of recovery after 3 months compared to those who were not supplemented. Daradkeh et al.[12] and Dubiel et al.[13] found 24% and 26% of TBI participants were deficient and an additional 67% and 36% of participants were insufficient, respectively. Neither study commented on differences between severities. Cut-offs for vitamin D deficiency varied between studies with < 10, 14, 16, and 30 ng/ml considered deficient. According to the Institute of Medicine, vitamin D deficiency is defined as serum 25 hydroxyvitamin D < 20 ng/ml.[49] The Endocrine Society Guidelines defines vitamin D insufficiency as serum 25 hydroxyvitamin D between 21-29 ng/ml.[50]

Research assessing testosterone and vitamin D status in military personnel following TBI is lacking, despite the evidence that these hormone deficiencies may exacerbate post-concussive symptoms. Furthermore, no research to date has examined testosterone replacement therapy following TBI. Therefore, the purpose of this study was to investigate testosterone and vitamin D concentrations in service members with and without a history of TBI to identify differences in these hormones as well as rates of testosterone replacement therapy. Incidence of post-TBI hypogonadism and vitamin D deficiency in military personnel helps to identify targets for therapeutic treatments to improve long-term recovery.

Goals

This retrospective study aims to investigate testosterone and vitamin D status in active duty and retired service members, with and without a history of traumatic brain injury, and the frequency of testosterone replacement therapy prescriptions.

Aim 1: We will investigate if service members with a history of TBI have lower testosterone concentrations than service members without prior injury.

Aim 2: We will investigate if service members with a history of TBI have lower vitamin D concentrations than service members without prior injury.

Aim 3: We will investigate significant correlations between testosterone and vitamin D concentrations with service members with and without a history of TBI.

Aim 4: We will investigate if service members with a history of TBI are more likely to have a testosterone replacement therapy prescription than service members without prior injury.

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Chapter 2: Article

Testosterone and Vitamin D Concentrations in Military Personnel Following Traumatic Brain Injury

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Abstract:

Background: Traumatic brain injury (TBI) has been shown to cause pituitary dysfunction, manifesting in low testosterone concentrations, and some research has shown vitamin D deficiency.

Purpose: To compare testosterone and vitamin D concentrations in active duty and veteran service members between those with and without a history of TBI, and to identify the frequency of testosterone prescriptions.

Materials and Methods: This retrospective de-identified medical review analyzed assessments (testosterone, vitamin D) ordered for 4,285 active duty and veteran military personnel at Womack Army Medical Center, Fort Bragg, NC from 2016-2018.

Results: Overall, 343 (8%) of service members had a medically diagnosed TBI. In all men, 19% were deficient in testosterone (< 270 ng/dl), and 10% had a testosterone prescription. Active duty men with a history of TBI had lower testosterone compared to active duty men with no documented head injury (431 ± 162 vs 452 ± 170 ng/dl, $p = 0.04$), but there was no significant difference in veteran men. More than one-third (38%) of all service members were insufficient in vitamin D (< 30 ng/ml). Overall there was a weak positive correlation between testosterone and vitamin D concentrations in men but not in women.

Conclusions: Our research does not support evidence for high rates of hypogonadism, testosterone prescription, or vitamin D deficiency after TBI compared to military personnel

without prior injury. However, our overall dataset shows a high prevalence of vitamin D insufficiency in both active duty and retired service members independent of TBI, further supporting that vitamin D status should be assessed regularly in service members.

Key Phrases: *traumatic brain injury; vitamin D; testosterone; testosterone replacement therapy; military personnel*

Conflict of Interest: No funding was secured for this study. The views expressed herein are those of the authors and do not reflect the official policy of the Department of the Army, Department of Defense, or the U.S. government.

Acknowledgments: We appreciate the Womack Army Medical Center Information Management Division for data acquisition.

Introduction

Traumatic brain injury (TBI) causes long-term consequences including degenerative diseases, psychiatric disorders and cognitive, behavioral, and physical defects that may prevent military personnel from performing to their greatest potential and negatively impacts long-term health.[1,2] Neuroendocrine dysfunction is a common consequence of TBI, as nearly half of all cases result in symptoms of neuroendocrine dysfunction.[3] Neuroendocrine dysfunction is the term for a variety of hormone imbalances directly related to the hypothalamus, pituitary and their axes.[4] Pituitary dysfunction, which manifests in low testosterone, is a biochemical deficiency in one or more endocrine axes by either an inadequate supply of hypothalamic-releasing hormones or the gland's inability to produce hormones.[5] Hypopituitarism with gonadotropin deficiency is one of the most prevalent types of neuroendocrine dysfunction following TBI and has been predicted to cause long-term secondary hypogonadism in up to 16% of individuals with a TBI diagnosis.[6,7] Although not normally tested with neuroendocrine disorders, vitamin D deficiency may be associated with TBI sequelae. Vitamin D's neuroprotective role following TBI has been explored in several studies, most of which have used an animal model.[8–15] It is unclear if TBI causes low vitamin D, but if vitamin D is low prior to TBI it may exacerbate injury.[8-16]

Numerous studies have shown a decrease in testosterone and vitamin D concentrations following TBI in civilians.[13,17-27] These studies have investigated mild, moderate, and severe TBI in relation to hypopituitarism, testosterone concentrations and vitamin D. Studies have shown severe hypopituitarism in all severities of TBI with hypogonadism being common, but low testosterone results have varied based on injury severity.[7] Four studies have investigated testosterone status in military personnel following

mild, moderate, and severe blast related TBI. These studies found low testosterone with injury with one study finding a significant decrease in testosterone 3 years after injury compared to controls.[3,28-30] Five civilian studies have investigated vitamin D status post-TBI and high rates of vitamin D deficiency were prevalent.[13,20,21,23,27] No differences between severities were found, with the exception of Toman et al.[27] who found the lowest vitamin D concentrations in the most severe cases of TBI.

Research assessing testosterone and vitamin D status in military personnel following TBI is lacking, despite the evidence that these hormone deficiencies may exacerbate post-concussive symptoms. Furthermore, no research to date has examined testosterone replacement therapy following TBI. Therefore, the purpose of this study was to compare testosterone and vitamin D concentrations between service members with and without a history of TBI and to identify rates of testosterone replacement therapy in this sample. Incidence of post-TBI hypogonadism and vitamin D deficiency in military personnel helps to identify targets for therapeutic treatments to improve long-term recovery.

Methods

Study Design & Procedures

This retrospective de-identified medical review investigated testosterone and vitamin D status in active duty and retired service members, with and without a history of traumatic brain injury, and the frequency of testosterone replacement therapy prescriptions.

Study Population

The study population included 4,285 veteran and active duty service members from the United States military who had serum testosterone and vitamin D ordered and assessed at Womack Army Medical Center (WAMC), Fort Bragg, NC between October 2016 and

December 2018. This protocol was approved by Appalachian State University Institutional Review Board and a letter of agreement was established with WAMC. Inclusion criteria was current or previous military service, male or female, aged > 18 years, with a serum testosterone assessment. Vitamin D was included in analysis if assessed at same time as testosterone. Additional data collected from medical records included diagnosis of TBI, prescription for testosterone replacement therapy, date of hormonal assessments, and participant demographics: age, sex and active duty/veteran military status.

Data Analysis

All analyses were conducted with the statistical software package, Stata 15 (StataCorp 2017). Independent T-tests were used to identify differences between continuous variables. Chi Square tests were used to identify differences between dichotomous variables. A one-way ANOVA with Bonferroni post hoc analysis was used to test for differences in vitamin D across seasons. Statistical significance was $p < 0.05$.

Results

Traumatic Brain Injury in Service Members

From 2016-2018, we identified 4,285 unique cases with testosterone assessments, of which 3,204 (75%) of participants were men, and 2,675 (62%) were active duty. Overall, 343 (8%) of service members and veterans were diagnosed with a TBI between October 2016 and September 2018. One hundred and ninety-eight service members had a mild or moderate TBI diagnosis, while 143 service members had a TBI of unknown severity. Active duty personnel had higher rates of TBI compared to veterans (12 vs. 2%, χ^2 (1, N = 4285) = 124, $p < 0.01$). Men were significantly more likely to be diagnosed with a TBI than women (10 vs. 1%, χ^2 (1, N = 4285) = 93, $p < 0.01$).

Testosterone Concentrations in Service Members

Overall mean total testosterone concentrations were 427 ± 179 ng/dl (range 5-800 ng/dl) for men and 31 ± 35 ng/dl (range 5-636 ng/dl) for women (Table 1). Of 3,204 men who were assessed, 19% were deficient in testosterone (< 270 ng/dl), and 10% had a testosterone prescription. Active duty men without testosterone prescriptions had significantly higher testosterone concentrations than active duty men with prescriptions (456 ± 163 vs. 365 ± 225 ng/dl, $t = 5$, $p < 0.001$). As expected, active duty men were younger with higher testosterone concentrations, lower rates of testosterone deficiency, and lower rates of testosterone prescriptions compared to veteran men (Table 1). Women were younger with lower testosterone concentrations and lower rates of testosterone prescription than men. Of the 1,081 women with testosterone assessments, n = 5 (3 active duty, 2 veteran) had high testosterone concentrations (279-636 ng/dl) but did not have testosterone prescriptions. Four women (1 active duty, 3 veteran) were prescribed testosterone, with similar formulations as those prescribed to male military personnel in this sample. Testosterone prescriptions consisted of gels, pellets, patches, and injections of low and high doses (range 2.5-200 mg of testosterone). However, the dose prescribed per day is not known.

In men with a history of TBI, 15% had a testosterone deficiency. However, men without TBI were more likely to have testosterone deficiency than men with history of TBI (19 vs 15%, χ^2 (1, N = 3204) = 4, $p < 0.05$); and there were no differences in testosterone prescriptions between men with and without TBI (7 vs 10%, χ^2 (1, N = 3204) = 3, $p = 0.068$). Although total testosterone concentrations in all men (activity duty and veteran) did not differ based on TBI history, active duty men with history of TBI had lower testosterone compared to active duty men with no documented head injury (Figure 1; 431 ± 162 vs 452 ±

170 ng/dl, t = 2, p = 0.035. This difference was not significant in veteran men (Figure 1; 418 ± 138 vs 353 ± 190 ng/dl, t = –2, p = 0.07). When men with testosterone prescriptions were excluded from analysis, active duty men with a history of TBI still had lower concentrations of testosterone than active duty men without TBI but not at a significant level (440 ± 158 vs 458 ± 163 ng/dl, t = 2, p = 0.07). There were no significant differences in testosterone concentrations in women with and without a history of TBI (28 ± 20 vs 31 ± 35 ng/dl, t = 0.50, p = 0.66).

Table 1. Service member's testosterone, vitamin D, and history of TBI by sex and military status.

	Active Duty Men *(n = 2427)*	**Veteran Men** *(n = 777)*	**Active Duty Women** *(n = 248)*	**Veteran Women** *(n = 833)*
Age (yrs)	37 ± 8[AC]	54 ± 12[B]	32 ± 8[B]	33 ± 10
TBI	n = 301 (12%)[ABC]	n = 30 (4%)	n = 9 (4%)	n = 3 (0.4%)
Testosterone (ng/dl)	450 ± 169[ABC]	356 ± 189[AB]	33 ± 42	30 ± 32
Testosterone Deficiency (<270 ng/dl)	n = 340 (14%)[C]	n = 259 (33%)		
Testosterone Prescriptions	n = 169 (7%)[ABC]	n = 155 (20%)[AB]	n = 1 (0.4%)	n = 4 (0.5%)
Vitamin D (ng/ml)†	35 ± 12[A]	35 ± 11[B]	33 ± 11	32 ± 12
Vitamin D Insufficiency† (<30 ng/ml)	n = 365 (35%)	n = 127 (38%)[B]	n = 39 (45%)	n = 127 (47%)

Data are presented as mean ± standard deviation for continuous variables †Not every subject had a vitamin D value (n = 1,742). [A]$p < 0.05$ vs active duty women. [B]$p < 0.05$ vs veteran women. [C]$p < 0.05$ vs. veteran men

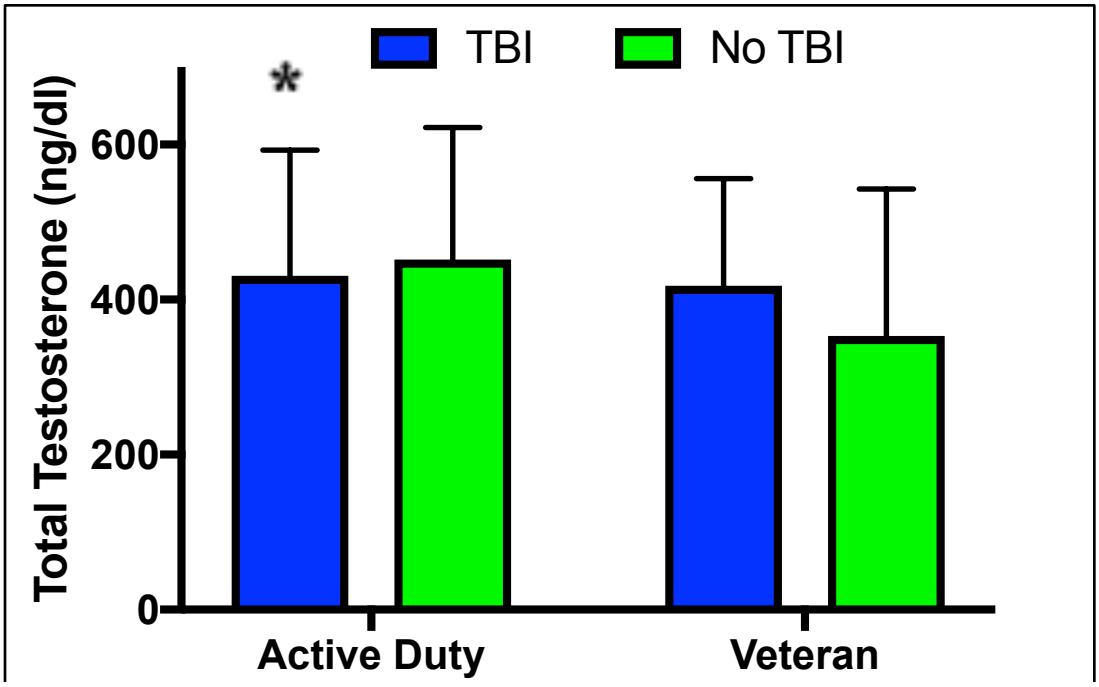

Figure 1. Testosterone concentrations in active duty and veteran men with and without a TBI. Data are presented as means ± standard deviation. *p < 0.05 significantly lower than active duty males without TBI.

Vitamin D Concentrations in Service Members

Overall mean vitamin D concentrations were 35 ± 12 ng/ml (range 8-60 ng/ml) for men and 32 ± 12 ng/ml (range 9-60 ng/ml) for women. Thirty-eight percent of all service members assessed were insufficient in vitamin D (< 30 ng/ml; 36% of men, 46% of women). One hundred and fifty-four service members (9%) were deficient in vitamin D (< 20 ng/ml). Active duty service members had higher concentrations of vitamin D compared to veterans (35 ± 12 vs. 33 ± 12 ng/ml, t = –3, p = < 0.01). Men had higher vitamin D concentrations compared to women (35 ± 12 vs. 32 ± 12 ng/ml, t = –4, p = < 0.001). Active duty men had higher concentrations of vitamin D compared to active duty women and veteran men had higher concentrations of vitamin D compared to veteran women (Table 1). There were no significant differences in vitamin D concentrations between active duty and veteran men or between active duty and veteran women (Table 1). Veteran women were significantly more

likely to have vitamin D insufficiency than veteran men, although there was no difference between active duty men and active duty women (Table 1). Season for vitamin D assay was evenly distributed: assessments were 24% in the spring, 23% summer, 29% fall, and 24% winter. Vitamin D concentrations were significantly different across seasons, hitting a nadir in winter and peak in summer ($F(3,1738) = 26$, $p < 0.001$; Figure 2). Vitamin D concentrations in winter (32 ± 11 ng/ml) were significantly lower than spring (35 ± 12 ng/ml), summer (38 ± 12 ng/ml) and fall (34 ± 11 ng/ml, $p < 0.001$). Summer vitamin D concentrations were higher than in the spring and fall, but there were no significant differences between fall and spring.

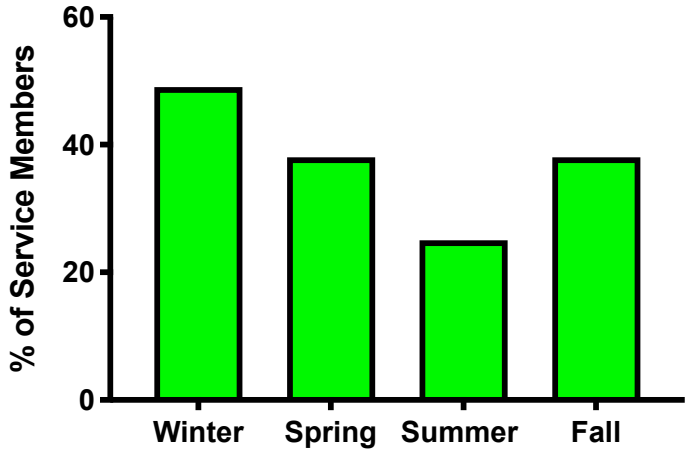

Figure 2. Percentage of service members insufficient in vitamin D (< 30 ng/ml) across each season: winter (December, January, February), spring (March, April May), summer (June, July, August), fall (September, October, November).

Contrary to our hypothesis, service members with a history of TBI had significantly higher concentrations of vitamin D compared to service members without a TBI (36 ± 12 vs. 34 ± 12 ng/ml, $t = –2$, $p < 0.05$), but the difference was minimal (2 ng/ml) and of little clinical significance. There was no significant difference in service members with and without TBI for vitamin D insufficiency (34 vs 38%, χ^2 (1, N = 1742) = 1, $p = 0.26$). Vitamin

D concentrations were not different between active duty or veteran service members with or without history of TBI (Figure 3).

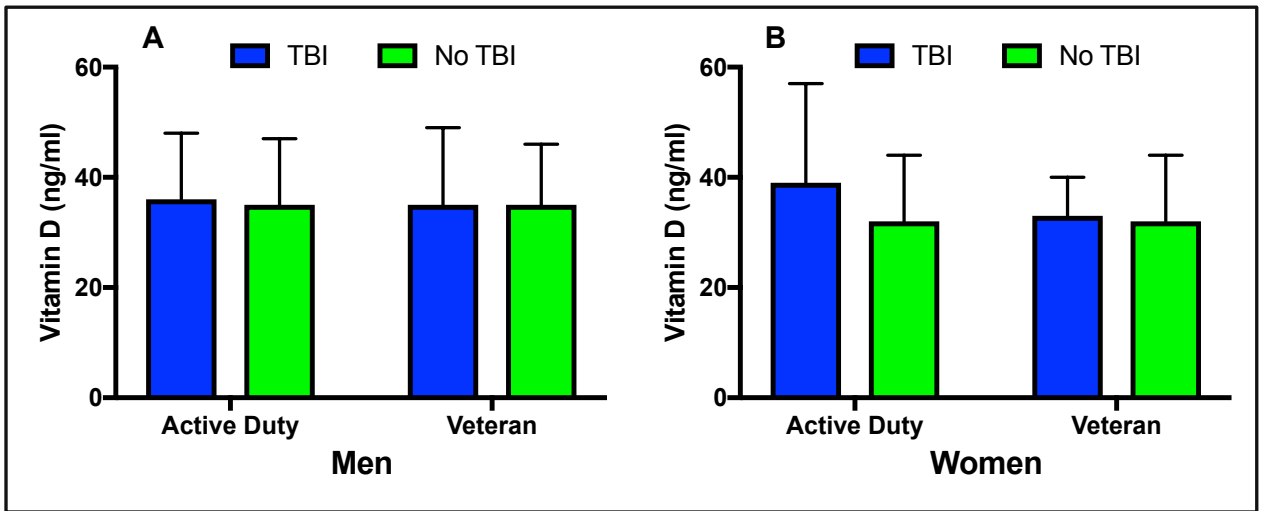

Figure 3. Vitamin D concentrations in active duty and veteran men (A) and women (B) with and without TBI. Data are presented as means ± standard deviation. There were no significant differences between groups.

Correlations between Testosterone and Vitamin D Concentrations in Service Members

Overall, there was a weak positive correlation between testosterone and vitamin D concentrations for men ($r = 0.099$, $p < 0.001$) but not for women ($r = 0.004$, $p = 0.94$). This significant correlation was maintained when compared among activity duty men ($r = 0.087$, $p = 0.005$) and veteran men ($r = 0.12$, $p = 0.028$). When men were analyzed separately by testosterone prescription, there was still a positive correlation between vitamin D and testosterone concentrations for men without testosterone prescriptions ($r = 0.095$, $p = 0.003$). No significant correlations were found in active duty or veteran women.

There was a weak positive but significant correlation between testosterone and vitamin D concentrations ($r = 0.099$, $p < 0.001$) for men without a TBI compared to men with a TBI ($r = 0.11$, $p = 0.12$) Likewise, active duty men without a TBI demonstrated a weak but significant positive correlation between testosterone and vitamin D concentrations

($r = 0.081$, $p = 0.018$), while active duty men with a history of TBI had no significant correlation ($r = 0.13$, $p = 0.076$). No significant correlations were found in active duty or veteran women with a TBI.

Discussion

TBI has been shown to cause low testosterone concentrations due to pituitary dysfunction and may have an effect on vitamin D status, but no published research to date has investigated both of these hormones in military personnel with TBI. In this retrospective analysis of medical records, we did not find higher rates of pituitary dysfunction or vitamin D deficiency in military personnel with a history of TBI compared to military personnel without prior injury. In our dataset, active duty men with a TBI had statistically lower testosterone compared to active duty men without prior injury, but the difference was small and of little clinical significance. No clinically meaningful relationship was observed between TBI and vitamin D deficiency. However, our overall dataset showed a high prevalence of vitamin D insufficiency in both active duty and retired service members independent of TBI. Correlations between testosterone and vitamin D concentrations were positive but weak in men. Perhaps these findings are driven by a low medically reported TBI diagnosis. Eight percent of military personnel in our sample had a TBI diagnosis, which is lower than previous research showing 15-23% of military personnel had been diagnosed with a TBI.[31-35] Our overall findings in military personnel do not support high prevalence of hypogonadism in men with history of TBI.

We found a lower prevalence of pituitary dysfunction (as evidenced by low testosterone) in men after TBI compared to previous studies that found 31-47.6% of military personnel to have some form of pituitary dysfunction, although not exclusive to

hypogonadism. However, our 15% rate of testosterone deficiency after TBI was similar or higher than other reported findings, ranging from 0-19%.[3,28-30] Contrary to these findings, civilian studies investigating pituitary dysfunction after TBI found higher rates of hypogonadism among participants (12.5-79%).[17-19,22,24-26] These findings suggest that blast-induced TBI may affect pituitary function differently than non-blast induced TBI, resulting in lower rates of hypogonadism.[28,30] Time post-injury and clinical cutoffs for testosterone deficiency also varied between both military and civilian studies. Nearly all of these studies used the 5th or 10th percentile of the sampled group to determine hormone deficiency (134-350 ng/dl). We used a conservative clinical cut-off of 270 ng/dl, which is used in the military medical system. Our results could have also been influenced by the length of time between the injury and the testosterone assessment, but our data did not allow for this analysis. Gonadotropin function has been shown to spontaneously resolve at 3 to 12 months after injury in a majority of patients due to temporary pituitary dysfunction from hypothalamic-pituitary edema, increased intracranial pressure, and the physiologic response to either critical illness or drugs used in the acute phase of TBI.[36-38] Our military personnel with TBI may have had testosterone deficiency but recovered prior to testosterone assessment and treatment, which would explain our low rates of hypogonadism. In addition, a negative correlation between testosterone concentrations and injury severity may exist in the immediate post-TBI period.[37] Perhaps more significant correlations would be evident in severe cases.[37,38] To our knowledge, this is the first study investigating testosterone prescription after TBI. We found no association between testosterone prescriptions and TBI diagnosis, which would coincide with the low rates of hypogonadism thus warranting fewer

prescriptions. Military treatment facilities have also become more conservative with prescribing testosterone replacement therapy.[39]

Semistarvation, inadequate sleep, and chronic anxiety during deployment have been shown to suppress testosterone levels in military personnel.[40,41] This finding may explain why active duty men with TBI had lower concentrations of testosterone compared to active duty men without injury while veterans with TBI did not have this result. Testosterone production may be reduced post-TBI as a result of inflammatory cascade cytokines suppressing Leydig cell function in the testes, leading to hypothalamic-pituitary-gonadal axis dysfunction.[42] Veterans with a TBI had higher testosterone than veterans without a TBI, but several veteran men without a TBI in our analysis had very low testosterone (< 10 ng/dl). This result is drastically lower than the age-related decline NHANES data has shown with participant's testosterone concentration at age 80 being 30% less than at age 20.[43] Interestingly, none of these testosterone deficient veterans were prescribed testosterone replacement therapy; assuming they did not show symptoms of androgen deficiency, this finding would be normal according to the Endocrine Society recommendations.[44] Another explanation for this finding could be influenced by the unknown length of time after injury since anterior pituitary trauma may result in normal or high serum concentrations of testosterone from the acute release of stored hormones after injury.[37]

Our findings on vitamin D concentrations support previous research in civilians and military personnel, showing that low vitamin D is a common ailment independent of TBI.[16,45-50] To our knowledge, this is the first study examining both testosterone and vitamin D concentrations in military personnel with and without TBI. Previous studies of civilians after TBI found similar rates of vitamin D deficiency compared to our finding (24-47% vs

34%).[20,23,27] However, the cut-off rates for these studies were lower than ours with < 10, 14, and 16 ng/ml being deficient. Two studies with an equivalent cut-off found much higher rates of deficiency at 63-95%.[13,21] Rates of deficiency could be influenced by the difference in latitude, clothing, race, and diet of the different countries in which these studies were conducted. The 35.1°N latitude of Fort Bragg allows for a long period of endogenous vitamin D synthesis, which would explain our lower rate of vitamin D deficiency after TBI.[51] Furthermore, insufficient racial data were available for analysis. Lastly, studies have shown mixed results between vitamin D concentrations and TBI severity. Jamall et al.[23] found no difference in vitamin D among TBI severities, while Toman et al.[27] found patients with severe TBI were the most deficient in vitamin D. Separate analysis of the most severe TBI cases may have shown higher prevalence of low vitamin D, but we did not have severity data for all cases. In this study, the seasonal distribution of vitamin D assessments was fairly evenly distributed throughout the year. In the United States, vitamin D seasonality peaks in August and nadirs in February, and during winter months UV radiation for most U.S. latitudes north of Atlanta, GA (33.7°N) is inadequate for sufficient endogenous synthesis of vitamin D.[16]

Our weak but positive correlation between vitamin D and testosterone in service men is consistent with previous findings by Wentz et al.[51], who found a stronger correlation in vitamin D deficient men. Contrary to these findings, one study found an increase in testosterone concentrations in active duty males during basic military training despite a significant decrease in vitamin D. The intense training and anabolic adaptations that occur during basic military training may explain the different findings in correlations between vitamin D and testosterone.[48] Vitamin D may be positively correlated with testosterone levels

in males due to the expression of the vitamin D receptor and metabolizing enzymes in the Leydig cells of the testes and has been shown to raise testosterone levels in vitamin D deficient men.[52,53] No correlation was found between vitamin D and testosterone in men with TBI possibly due to a lower sample size given that no difference was discovered in vitamin D between men with and without injury.

We did not find evidence that TBI causes low vitamin D, but other research suggests that low vitamin D may exacerbate injury. Vitamin D may promote resilience after TBI by regulating calcium ions, oxidative stress, inflammation, excitotoxicity and apoptosis during the secondary cascade of injury.[13,14] Cui et al.[10] found that calcitriol treatment can improve neurobehavioral defects and cerebral edema in rats after TBI. Progesterone treatment combined with vitamin D supplementation after TBI has shown better results in animal studies than progesterone alone through maintained spatial and reference memory, diminished neuronal loss and astrogliosis, and improved treatment efficacy.[8,12,15] Cekic et al.[8] found vitamin D deficient rats had increased baseline brain inflammation and no benefit from progesterone treatment compared to vitamin D sufficient rats. In human trials, one clinical trial found a combined treatment of progesterone and vitamin D had higher rates of recovery than progesterone alone, while another study found vitamin D supplementation singlehandedly increased long-term performance and cognitive outcomes vitamin D deficient patients with mild-to-moderate TBI. [13,54]

Our overall dataset shows a high prevalence of vitamin D insufficiency. Since military personnel are at high risk for TBI and tactical gear limits adequate sunlight exposure, it is recommended to assess vitamin D status biannually.[55] It would be beneficial to supplement those with insufficiency and deficiency accordingly to Endocrine Society

Guidelines to maintain optimal vitamin D levels as a preventive measure to improve resiliency post-TBI.[56] Since gonadotroph function may spontaneously recover in 3 to 12 months after injury, endocrine evaluation should be completed at 3 to 6 months and re-assessed at 12 months post-TBI.[57,58]

This study was strengthened by a large set of medical records that were reviewed for one geographical location, which limited the effect of latitude. Limitations of this study include the observational nature of the medical record review in which causal relationships cannot be established, only correlations. Furthermore, data for confounding variables such as race, sex hormone binding globulin, training status, dietary supplements, length of time after injury, and body composition were not available for analysis. Lastly, this sample consists of military personnel who had vitamin D and testosterone ordered by a physician and is not representative of all service members.

Our research does not support evidence for high rates of hypogonadism, testosterone prescription, or vitamin D deficiency after TBI compared to military personnel without prior injury. However, our overall dataset shows a high prevalence of vitamin D insufficiency in both active duty and retired service members independent of TBI, further supporting that vitamin D status should be assessed regularly in service members. A prospective analysis pre-injury may provide better insight into the role of testosterone and vitamin D in TBI.

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Age (yrs)	37 ± 8^{AC}	54 ± 12^{B}	32 ± 8^{B}	33 ± 10
TBI	n = 301 (12%)^{ABC}	n = 30 (4%)	n = 9 (4%)	n = 3 (0.4%)
Testosterone (ng/dl)	450 ± 169^{ABC}	356 ± 189^{AB}	33 ± 42	30 ± 32
Testosterone Deficiency (<270 ng/dl)	n = 340 (14%)^{C}	n = 259 (33%)		
Testosterone Prescriptions	n = 169 (7%)^{ABC}	n = 155 (20%)^{AB}	n = 1 (0.4%)	n = 4 (0.5%)
Vitamin D (ng/ml)†	35 ± 12^{A}	35 ± 11^{B}	33 ± 11	32 ± 12
Vitamin D Insufficiency† (<30 ng/ml)	n = 365 (35%)	n =127 (38%)^{B}	n = 39 (45%)	n = 127 (47%)

Data are presented as mean ± standard deviation for continuous variables †Not every subject had a vitamin D value (n = 1,742). $^{A}p < 0.05$ vs active duty women. $^{B}p < 0.05$ vs veteran women. $^{C}p < 0.05$ vs. veteran men

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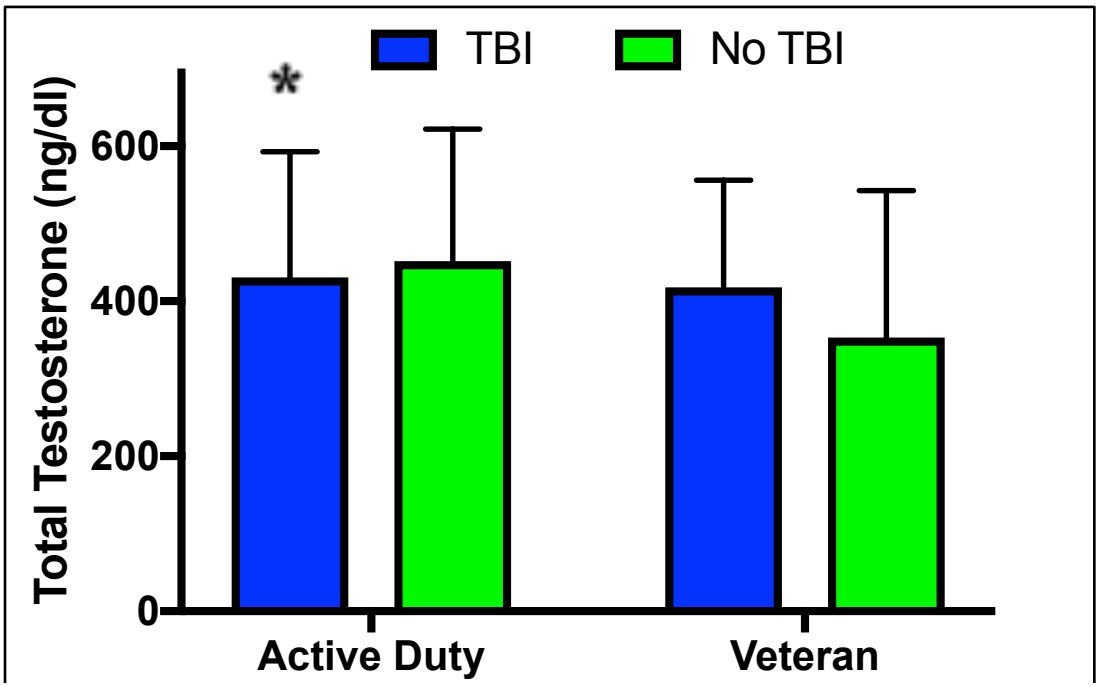

Figure 1. Testosterone concentrations in active duty and veteran men with and without a TBI. Data are presented as means ± standard deviation. *p < 0.05 significantly lower than active duty males without TBI.

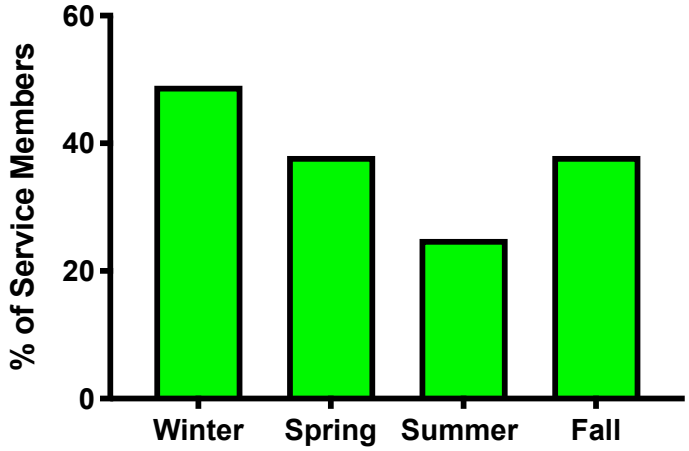

Figure 2. Percentage of Service Members Insufficient in Vitamin D (< 30 ng/ml) Across Each Season: Winter (December, January, February), Spring (March, April May), Summer (June, July, August), Fall (September, October, November),

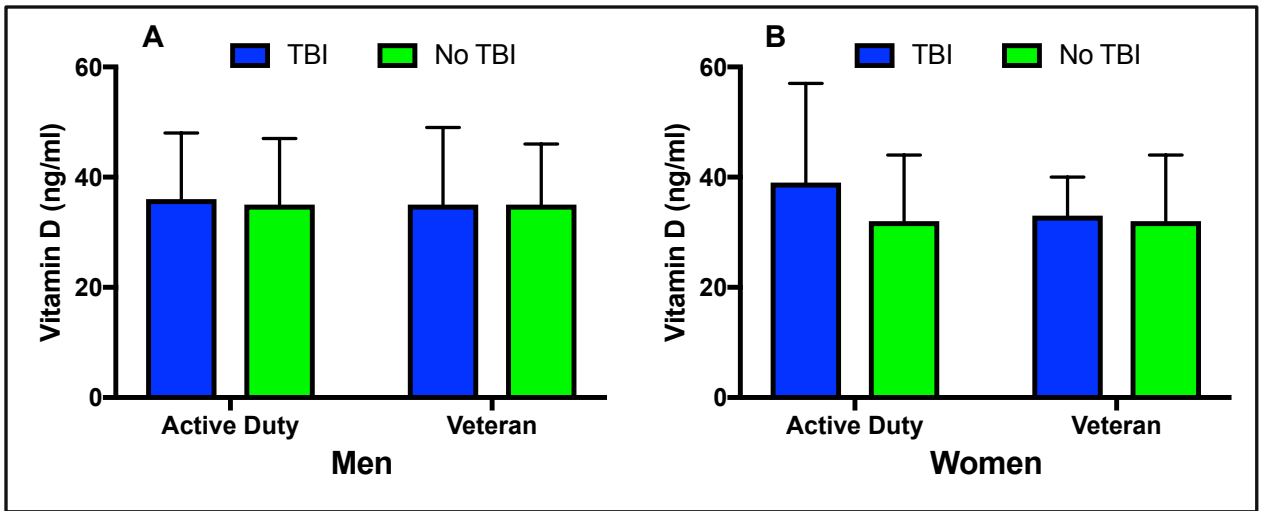

Figure 3. Vitamin D concentrations in active duty and veteran men (A) and women (B) with and without TBI. Data are presented as means ± standard deviation. There were no significant differences between groups

Vita

Kelsey C. Tillotson was born in Tampa, Florida, to Jacqueline E. Tillotson and Dr. Kenyon F. Tillotson. She graduated from Berkeley Preparatory School in 2013, after which, she attended Appalachian State University where she received a Bachelor of Science in Dietetics in 2017. She completed an internship at Walt Disney World in the Fall of 2017, and she will be awarded the Master of Science degree in Nutrition and Dietetics in May of 2020 from Appalachian State University.