Vitamin D insufficiency increases risk of chronic pain among African Americans experiencing motor vehicle collision

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Abstract

African Americans experience an increased burden of motor vehicle collision (MVC), post-MVC musculoskeletal pain, and vitamin D insufficiency. In this prospective multicenter study, we tested the hypothesis that African Americans (n = 133) presenting to the emergency department after MVC with low peritraumatic vitamin D levels would have worse chronic musculoskeletal pain outcomes compared to individuals with sufficient vitamin D. Vitamin D levels were assessed in the early aftermath of MVC through enzyme-linked immunosorbent assay, and pain severity was assessed using the 0 to 10 numeric rating scale at 6 weeks, 6 months, and 1 year. In repeated-measures analysis, African American MVC survivors with vitamin D insufficiency experienced more severe chronic pain ($\beta = 1.18$, $P = 0.031$). In secondary analyses, we assessed for evidence that the effect of vitamin D on post-MVC pain outcomes is mediated, at least in part, by the influence of vitamin D on genetic variants in genes involved in immune system regulation (*IL-10* and *NLRP3*). Genotyping was performed using a genome-wide microarray using collected DNA samples. Secondary analyses suggest that the effect of vitamin D on post-MVC pain outcomes may be influenced by genetic variation in *IL-10* and *NLRP3*. Further studies are needed to assess the impact of vitamin D insufficiency on pain outcomes in African Americans experiencing MVC and other common trauma exposures, to assess factors affecting this relationship, and to assess the efficacy of administering vitamin D in the immediate aftermath of MVC to prevent chronic pain. Such low-cost, nonopioid interventions are urgently needed to address chronic pain development after MVC.

Keywords: Motor vehicle collision, Persistent pain, Vitamin D3, Cholecalciferol, African Americans, Chronic pain

1. Introduction

Motor vehicle collisions (MVCs) result in 50 million injuries worldwide and almost 4 million U.S. emergency department (ED) visits each year.[45,58] In the United States, approximately 90% of individuals presenting to the ED after MVC are discharged to home after evaluation.[49] Chronic musculoskeletal pain (MSP) after MVC in this population is a common and costly public health problem.[5]

African Americans experience an increased burden of MVCs compared to European Americans,[1] and compared to European Americans, African Americans have been found to experience an increased burden of MSP across a range of conditions, including cancer,[2,27] osteoarthritis,[6,14] and low back pain.[4,7] African Americans experience a marked socioeconomic disadvantage compared to European Americans,[25,51,55] which may contribute to the increased burden of chronic MSP in African Americans experiencing MVC. Despite these socioeconomic differences, available evidence suggests that worse health outcomes in African Americans are not due to socioeconomic differences alone.[9,48,63,64]

One biological factor that may contribute to chronic post-MVC MSP in African Americans experiencing MVC is low vitamin D levels. Even after adjusting for socioeconomic status, vitamin D insufficiency disproportionately burdens African Americans.[19,52,62] In population-based studies, 24% to 86% of African Americans are vitamin D deficient, vs only 2.3% to 40% of

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European Americans.[16,19,54,61] Putative mechanisms by which low vitamin D levels may augment post-MVC MSP vulnerability include via altering the activity of the NLRP3 inflammasome, a critical cytosolic molecular complex implicated in MSP pathogenesis that regulates inflammation,[31,32,60] and via modulating levels of the anti-inflammatory cytokine IL-10.[18,26,43,44]

In this prospective multicenter study, we tested the hypothesis that African Americans presenting to the ED after MVC with low peritraumatic vitamin D levels would have worse chronic MSP outcomes compared to individuals with sufficient vitamin D. In secondary analyses, we tested the hypothesis that genetic polymorphisms identifying influential segments of genes encoding NLRP3 and IL-10 would interact with low vitamin D to influence chronic pain severity after MVC. If substantial effect modification were present between vitamin D insufficiency and genetic subgroups with differences in NLRP3 and IL-10 function, this would suggest that vitamin D insufficiency influences long term posttraumatic MSP outcomes by affecting these pathways.

2. Methods

2.1. Study design and participants

Participants included in this analysis (n = 133) were drawn from a prospective, multicenter ED-based observational cohort study, previously described in detail,[36] which enrolled participants within 24 hours of MVC and evaluated pain and functional outcomes 6 weeks, 6 months, and 1 year after MVC. Study recruitment flow diagram is shown in Supplemental Figure 1 (available at http://links.lww.com/PAIN/A894). All included participants followed up at 6 weeks, 121/133 (91%) followed up at 6 months, and 118/133 (88%) at 1 year. The majority (112/133, 84%) of patients followed up at all timepoints, and 6 patients were lost to follow-up after the 6 week timepoint. Samples analyzed were from participants enrolled across 6 EDs in 2 no-fault insurance states in the United States (Pennsylvania and Michigan). Recruitment took place between July 2012 and March 2014. Institutional review board approval was obtained at each study site, and each participant provided written informed consent before enrollment. Enrolled participants provided plasma samples, and available samples were submitted for vitamin D analysis.

Eligible patients were alert, oriented, English-speaking African Americans aged 18 to 65 years who presented to one of the study site EDs for evaluation after MVC. Patients with spinal fracture/dislocation, or neurologic signs including decreased/absent deep tendon reflexes or weakness, skull fracture, facial fracture, intracranial injury, long bone fracture, or laceration with significant hemorrhage, and those presenting more than 24 hours after injury were excluded, as were prisoners, pregnant patients, individuals unable to read and understand English, individuals who were clinically unstable or who had potentially life-threatening injuries, and individuals who were patients on chronic opioids (above a daily dose of 30 mg of oral daily morphine equivalents). It was not a requirement to have pain to participate in the study.

2.2. Measurements

Demographic information was collected at the time of enrollment. Pain severity was assessed at enrollment through in-person interview and at 6 weeks, 6 months, and 1 year by telephone interview. Overall pain was assessed using a 0 to 10 numeric rating scale (NRS) in which participants were asked to rate their overall pain on a 0 through 10 Likert scale with 0 representing "no pain" and 10 "maximal possible pain."[15] At baseline, patients reported current pain intensity, whereas at follow-up timepoints, participants reported pain over the past week (0-10 NRS). The regional pain scale[66] was used to assess the number of body regions with moderate or severe pain related to the MVC. The American College of Rheumatology 1990[65] criteria were used to calculate the proportion of individuals with widespread pain based on results of the regional pain scale. Severe axial pain was defined as pain that was rated as ≥7/10 in intensity in at least one axial body region including the neck, upper back, lower back, and right or left shoulder.[37]

2.3. Plasma sample collection and vitamin D assessment

Plasma was collected from study participants at the time of initial assessment in the ED using a previously described, standardized protocol.[36] Plasma samples were stored at −80°C and thawed immediately before analyses. After 1:26 dilution, plasma concentrations of 25-hydroxyvitamin D were analyzed using an enzyme-linked immunosorbent assay (ELISA) (Eagle Bioscience, Nashua, NH). Analyses were performed in duplicates; reliability was evaluated by calculating the coefficient of variation (%CV), and %CV less than 10% was considered acceptable.

2.4. Primary predictor definition

Based on accepted guidelines that suggest that levels greater than or equal to 30 ng/mL are considered sufficient and levels less than 30 are considered insufficient,[29,30,50] and that therapies to address vitamin D insufficiency target levels above 30 ng/mL,[29,50] we categorized individuals with 25-hydroxyvitamin D values greater than or equal to 30 ng/mL as vitamin D sufficient.

2.5. DNA collection and genotyping

Blood samples were collected at the time of enrollment using PAXgene DNA tubes. After DNA purification (PAXgene blood DNA kit; QIAGEN, Venlo, the Netherlands), genotyping using the Infinium Multi-Ethnic Global Array (Illumina, San Diego, CA) was performed. DNA from an individual with known genotype (NA19819, 1000 genomes) and 2 repeat samples were included in each genotyping batch (96 samples) to ensure genotypic accuracy and reliability. All tested single-nucleotide polymorphisms (SNPs) were in Hardy–Weinberg equilibrium ($P > 0.05$) and had an excellent call rate (>99%). Single-nucleotide polymorphisms were chosen for analysis based on one of the following 2 criteria: (1) they were previously defined to play a role in neuropsychiatric or inflammatory conditions: NLRP3: rs10754558,[34] rs4353135,[67] rs10925027[24]; IL10: rs3024505,[17] rs1800871,[10] rs1800896,[20] rs1800893,[39] rs1878672,[20] rs1518111;[39] or (2) they were identified as tag SNPs using the TagSNP feature from the National Institute of Environmental Health Sciences website (https://snpinfo.niehs.nih.gov/snpinfo/snptag.html).

2.6. Statistical analyses

Descriptive statistics were used to summarize baseline patient characteristics. Patients were then categorized into vitamin D insufficient (<30 ng/mL) and vitamin D sufficient (≥30 ng/mL) groups. A linear mixed-effects model with correlated error terms (using the unstructured covariance matrix, selected from optimizing Akaike information criteria) was used to evaluate the association between vitamin D status at the time of injury and pain severity at week 6, month 6, and year 1 after adjusting for age,

sex, study site, education attainment, income and time since injury. Mixed-effects analyses were performed using SAS 9.4 (SAS Institute, Inc, Cary, NC). *P*-values <0.05 were considered statistically significant. Missing values were not imputed.

In SNP analysis, the dominant genetic model was used because (1) it enables testing of our hypothesis that presence of the minor allele confers risk or protection from chronic pain and (2) has been used extensively to examine gene and gene by environment interactions in previous studies of trauma populations.[35,38,40] Use of one genetic model also confers the advantage of preventing inflated type I error rates caused by testing multiple models and choosing the model post hoc.[56] Repeated-measures regression analysis clustered by participant and adjusted for age, sex, study site, income, education attainment, and time since injury was used to determine whether there was a significant interaction between vitamin D status at the time of injury and presence of the minor/"risk" allele. Mean chronic pain severity (0-10 NRS) for those with and without the minor allele were obtained from repeated-measures regression models. Stata 14 was used for SNP analysis (College Station, TX). Scatterplots and best-fit lines for supplemental figure 2 was created using GraphPad Prism 7.04 (San Diego, CA) (available at http://links.lww.com/PAIN/A894).

Matrix Spectral Decomposition (matSpD) of the correlation matrix of 21 SNPs was used to calculate the total number of effective comparisons adjusting for linkage disequilibrium.[46] This method yielded an SNP experiment-wide significance threshold of 0.0034 to maintain type I error rate at 5%.

3. Results

3.1. Participant characteristics

Participant characteristics (n = 133) are summarized in **Table 1**. Most participants were women younger than 40 years of age who earned $40,000 per year or less and had completed high school. Acute severe MSP after MVC was the norm; 80/128 (63%) of study participants rated their MSP severity as ≥7 in the ED. Moderate or severe MVC-related pain was present in at least one body region in 104/133 (78%) at 6 weeks, 83/120 (69%) at 6 months, and 61/118 (52%) at 1 year. The most common sites of moderate or severe chronic pain over the 1 year after MVC were the lower back, upper back, and neck. For example, 6 months after MVC, 59% (71/120) experienced lower back pain, 41% (49/120) experienced upper back pain, and 36% (43/120) experienced neck pain. Axial pain and widespread pain were both common after MVC with 33% (40/121) experiencing widespread pain and 39% (47/121) experiencing severe axial pain.

3.2. Participant vitamin D status and association with sociodemographic characteristics

Study participant ED vitamin D levels ranged from 4.2 to 79.7 ng/mL, with median and mean (SD) levels of 21.9 ng/mL and 24.4 ng/mL (11.7 ng/mL), respectively. Vitamin D insufficiency (≤30 ng/mL) was present in 77% (103/133) of study participants. Age and sex were associated with vitamin D status such that study participants with vitamin D insufficiency were more likely to be younger females (**Table 2**). Participant education and income were not associated with vitamin D status (**Table 2**).

3.3. Association between vitamin D level and pain severity after motor vehicle collision

Mean pain scores over time among vitamin D sufficient and insufficient participants are shown in **Figure 1**. In repeated-measures analysis adjusting for age, sex, and time (weeks), participants with vitamin D insufficiency experienced more severe overall pain over time than individuals with sufficient vitamin D levels ($\beta = 1.18$, $P = 0.031$). Scatterplots of chronic pain severity (0-10 NRS) vs 25-hydroxyvitamin D concentration are shown along with best-fit lines in Supplemental Figure 2 (available at http://links.lww.com/PAIN/A894). At no timepoint were there a significant linear fit.

3.4. Interaction of vitamin D status and single-nucleotide polymorphisms in the IL10 gene on chronic pain severity

Vitamin D status and presence of the minor allele at rs3024505 interacted to influence chronic pain severity (**Table 3**). In the absence of vitamin D insufficiency, after adjustment for multiple comparisons, the presence of the minor allele at rs3024505 predicted more severe overall pain over time (7.3 vs 3.9, $P = 0.023$). By contrast, in the presence of vitamin D insufficiency, presence of the minor allele predicted less severe overall pain (2.9 vs 5.3, $P = 0.031$). No significant interactions were observed between vitamin D status and the other 5 IL-10 SNPs assessed (rs1800871, rs1800896, rs1800893, rs1878672, and rs1518111, Supplemental Table 1, available at http://links.lww.com/PAIN/A894).

Table 1

Patient characteristics between groups based on vitamin D status.

Variable	All (n = 133)	Vitamin D status		*P*
		Insufficient (n = 103)	Sufficient (n = 30)	
Patient age (95% CI)	35.5 (12.5)	33.9 (31.6-36.3)	40.8 (35.6-45.9)	0.010
Female (%)	84 (63%)	72/103 (70%)	12/30 (40%)	0.005
Education level				0.512
<8 y	1 (0.8%)	1 (1%)	0 (0%)	
8-11 y	13 (10%)	10 (10%)	3 (10%)	
12 y	46 (35%)	33 (32%)	13 (43%)	
Post high school	73 (55%)	56 (57%)	13 (47%)	
Income level				0.186
0-19,999	33 (33%)	25 (33%)	8 (35%)	
20,000-39,999	32 (32%)	28 (36%)	4 (17%)	
40,000-59,999	18 (18%)	14 (18%)	4 (17%)	
≥60,000	17 (17%)	10 (13%)	7 (30%)	

Vitamin D insufficiency defined as 25[OH] vitamin D plasma levels <30 ng/mL.
CI, confidence interval.

Table 2

Repeated-measures, mixed regression model of chronic pain severity over time after motor vehicle collision (n = 133).

Effect	Coefficient estimate	SE	95% CI
Vitamin D insufficiency* (ref = absent)			
Present	1.18	0.54	0.11 to 2.25
Patient sex (ref = Male)			
Female	0.55	0.51	−0.45 to 1.56
Income	0.005	0.01	−0.01 to 0.02
Education attainment	−0.21	0.17	−0.54 to 0.12
Patient age	0.04	0.02	−0.001 to 0.07
Weeks since injury	−0.03	0.005	−0.04 to 0.02

Mixed-effects model with random intercepts, adjusted for age, sex, education, income, study site, and weeks since injury (study site estimates not shown), *P*-values for a t-statistic are 2-tailed.
*25-hydroxyvitamin D plasma levels <30 ng/mL defined as insufficiency.
CI, confidence interval.

3.5. Interaction of vitamin D status and single nucleotide polymorphisms in the NLRP3 gene on chronic pain severity

Vitamin D status and presence of the minor allele at rs10925027 interacted to influence chronic pain severity (**Table 3**). In the absence of vitamin D insufficiency, after adjustment for multiple comparisons, the presence of the minor allele at rs10925027 predicted lower chronic pain severity after MVC (3.1 vs 5.7, $P < 0.001$). However, in the presence of vitamin D insufficiency, this protective effect was not observed. After adjustment for multiple comparisons, no significant interactions were observed between vitamin D status and the other 2 NLRP3 SNPs assessed (rs10754558 and rs4353135, Supplemental Table 2, available at http://links.lww.com/PAIN/A894).

4. Discussion

In this multicenter study, African Americans with vitamin D insufficiency at the time of initial emergency evaluation had more severe MVC-related MSP during the year after MVC. This finding is unlikely to be due to differences in socioeconomic status because vitamin D insufficiency in the study sample was not associated with socioeconomic status (consistent with available literature[62]) and study analyses were adjusted for sociodemographic factors. As with previous studies, we found that younger age and female sex were associated with lower vitamin D levels.[21,54] Study findings are clinically important because vitamin D supplementation, medications targeted at vitamin D signaling pathways may represent a nonopioid analgesic intervention in African Americans, a group who experience an increased burden of MVC,[1] who experience a greater burden of pain after MVC,[3] and in whom vitamin D insufficiency is present in up to 70%. If vitamin D supplementation at the time of ED evaluation improves chronic pain outcomes in this high risk group, this simple low-cost intervention could itself decrease chronic pain 6 months after MVC by 10%. This equates to approximately 70,000 fewer cases of chronic pain annually among African Americans experiencing MVC based on national data. Although the data presented are promising, causality cannot be determined by this small, observational study and future prospective randomized controlled trials are needed.

The results of this study are consistent with findings from several previous cross-sectional studies that found lower vitamin D levels are associated with an increased incidence and/or severity of chronic regional or widespread MSP.[22,28,47] These studies include a previous study by Glover et al.[22], which found that osteoarthritis patients with vitamin D insufficiency had higher pain sensitivity. Interestingly, this effect of vitamin D insufficiency on pain sensitivity was increased in African Americans vs European Americans.[22] Previous work in osteoarthritis suggests an interaction between obesity and vitamin D to influence function;[23] however, in our analyses we did not find a significant interaction or that adjusting for body mass index causes significant variation in model estimates. In contrast to previous work demonstrating an association between vitamin D and pain, 2 other studies failed to show an association between vitamin D levels and MSP,[12,57] perhaps because of small sample size[57] and/or a low prevalence of vitamin D insufficiency.[12]

Results of secondary analyses provide preliminary support for the hypothesis that the effect of vitamin D levels on pain outcomes may be mediated, at least in part, by genetic variants in the genes encoding NLRP3 and IL-10, 2 proteins that regulate immune system function. We examined SNPs in the *NLRP3* gene because NLRP3 is a key component of the inflammasome, and is a master regulator of innate immunity.[11] NLRP3 has been associated with

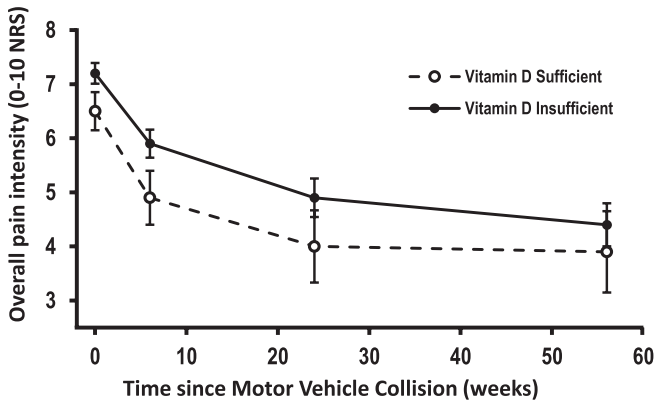

Figure 1. Overall pain intensity over time after MVC in individuals who are vitamin D insufficient (closed circles) vs those with normal vitamin D insufficiency (open circles). Error bars drawn around each data point represent the standard error of the mean. Although there are no statistically significant differences among mean pain intensity with respect to vitamin D status at each individual timepoint, a repeated-measures mixed model, adjusted for age, sex, and time since MVC indicates a significantly increased pain among individuals with vitamin D insufficiency ($\beta = 1.18$, 95% CI = 0.11-2.25). CI, confidence interval; MVC, motor vehicle collision; NRS, numeric rating scale.

Table 3

Interaction of vitamin D status with single-nucleotide polymorphisms in *IL10* and *NLRP3* on mean overall chronic pain severity in African Americans after motor vehicle collision

Vitamin D status	*Gene*: SNP	Gene function	Minor allele (N)	N	Mean pain NRS	95% CI	*P*	Interaction *P*
Sufficient	*IL10*: rs3024505	IL 10 is an anti-inflammatory cytokine.	Absent	27	3.9	3.1-4.7	0.023	0.002
			Present	3	7.3	4.4-10.2		
Insufficient			Absent	97	5.3	4.8-5.8	0.031	
			Present	4	2.9	0.8-5.0		
Sufficient	*NLRP3*: rs10925027	NLRP3 is a master regulator of inflammation including IL1β production.	Absent	12	5.7	4.6-6.9	<0.001	0.001
			Present	18	3.1	2.3-4.0		
Insufficient			Absent	27	4.8	4.1-5.6	0.336	
			Present	74	5.3	4.7-5.9		

Repeated-measures regression model (6 weeks, 6 month, and 1 year) using dominant genetic model adjusted for sex, age, study site, education attainment, income, and time since injury. All SNPs have a call rate >99% and are in Hardy–Weinberg equilibrium. Experiment-wide significance threshold determined by matSpD is 0.0034.
CI, confidence interval; NRS, numeric rating scale; SNP, single-nucleotide polymorphism.

chronic pain in preclinical models,[31,32] generates proinflammatory mediators[11] (eg, IL-1β) that worsen pain, and is influenced by vitamin D levels.[60,68] Among African American MVC survivors, the (protective) minor allele at *NLRP3* rs10925027 predicted lower post-MVC pain severity only in those with sufficient vitamin D. We examined SNPs in the *IL-10* gene because IL-10 is an important anti-inflammatory cytokine[18,26,43,44] and is associated with chronic pain.[43,44] *IL-10* SNP rs3024505 is downstream from the *IL-10* promoter[42] and has been localized to a vitamin D receptor binding interval.[53] The minor allele at SNP rs3024505 was protective from chronic pain in vitamin D insufficiency but conferred pain vulnerability in the presence of vitamin D sufficiency. Further work to assess the potential influence of vitamin D on the expression and/or function of genes that regulate immune system function is needed. Future studies should also examine the extent to which these immune genes potentially regulate vitamin D synthesis and/or metabolism.

4.1. Limitations

Several limitations should be considered when interpreting the study results. First, our sample size of 133 participants is relatively small. However, our study is larger than vitamin D association studies in other pain conditions,[13,47,59] and a difference in vitamin D groups was observed. Second, our study only includes African Americans who experienced MVC, and cannot be generalized to other ethnicities. However, African Americans are a markedly understudied ethnicity in pain investigations, and experience an increased burden of vitamin D insufficiency. Third, vitamin D insufficiency cannot be deemed a causal factor for chronic pain development based on the results of this observational study. Fourth, the nature of the relationship of vitamin D to pain, or to other clinical outcomes, is unknown and has not been studied (eg, if it is linear, quadratic, etc.). Rather, a clinical threshold is widely used, with analyses comparing vitamin D sufficient and vitamin D insufficient individuals. In support of this approach, a plateau effect above this threshold has indeed been identified for other clinical outcomes (eg, bone health[29,41]). We used this cutoff in this study, but provide crude scatterplots of vitamin D vs pain outcomes as Supplemental Figure 2 (available at http://links.lww.com/PAIN/A894), to provide information to readers as these data from additional studies continue to accrue. Finally, the effect of initial vitamin D levels on chronic pain severity may be confounded by unmeasured variables such as sun exposure, dietary intake of vitamin D fortified foods, and seasonal variation.[8] Vitamin D levels are influenced by light exposure as skin exposure to ultraviolet radiation facilitates conversion of 7-dehydrocholesterol to vitamin D_3.[30] It is also possible that vitamin D level is proxy for an unmeasured causal factor, such as UV light exposure, which may reduce pain in a vitamin D independent manner. This leads to seasonal variation in vitamin D levels.[33] Vitamin D levels are also influenced by intake from natural and fortified foods.[30] Future studies should examine these factors in relationship to vitamin D levels and pain severity.

5. Conclusions

In this multicenter study, African Americans with vitamin D insufficiency at the time of initial emergency evaluation had more severe MVC-related MSP during the subsequent year. Secondary analyses suggest that the effect of vitamin D on post-MVC pain outcomes may be mediated, at least in part, by the influence of vitamin D on the expression and/or function of proteins that regulate immune system function. Study findings are important because African Americans experience an increased burden of both MVC and post-MVC MSP, and vitamin D supplementation in the immediate aftermath of MVC is a potential low-cost, nonopioid intervention.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Appendix A. Supplemental digital content

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