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LTG R. Scott Dingle
The Surgeon General
Commander
US Army Medical Command

MG Dennis P. LeMaster
Commander
US Army Medical Center of Excellence

GEN Paul E. Funk II
Commander
US Army Training & Doctrine Command

Edward A. Lindeke
Executive Director
Borden Institute

Lyndon Crippen-Gonzalez
Chief Editor
The Medical Journal

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Note from the Editor...

Happy New Year and welcome to 2022! We hope you and your family enjoyed the holiday celebrations and are ready to begin again a new year that promises to be full of discovery and opportunity.

And speaking of discovery, this first issue of 2022 is dedicated to research and readiness. In the world of military medicine, these two topics are inseparable, with each adding to the depth, importance, and necessity of the other. We hope you enjoy the diverse subject matter included in this spring issue. Maybe it will ignite a spark for some to dust off the computer and draft a manuscript of your own to submit to *The Medical Journal.*

The Medical Journal accepts submissions year round. Included in each issue is a copy of the submission guidelines. Find more information about the journal and view electronic issues online at https://medcoe.army.mil/the-medical-journal.

The Medical Journal also has a new call for submissions for all things related to military veterinary medicine. View the call for submissions on the journal's website and be sure to share with friends and colleagues who might be interested.

Agencies or organizations interested in doing a special topic issue, please contact *The Medical Journal* to discuss your ideas and the details involved by emailing usarmy.jbsa.medical-coe.list.amedd-journal@army.mil.

Military Medical Readiness and Patient Experience with Access to Care

Beatrice Abiero, PhD
Melissa Gliner, PhD
Sharon Beamer, AuD
Amanda Sackett, MPH
Kimberley Marshall-Aiyelawo, PhD, CDR, MSC, USN (ret)
Janice Ellison, MA, SMSgt, Nursing Services, USAF (ret)
Terry McDavid
John de Geus, MD, LCDR, MC, USN

Abstract

Introduction: Medical readiness is an integral component of total readiness and a prime indicator of an individual's overall fitness to deploy. Promoting medical readiness is the prime directive for military medical departments; however, there are few studies evaluating specific factors of care delivery that will improve medical readiness. In this study, we evaluated one of the common patient perceptions that access to routine and specialty care will have a positive effect on military medical readiness. Surprisingly, there appeared to be a reverse relationship between a patient's perception of access to care and the correlation to their medical readiness.

Materials and Methods: This study uses the Joint Outpatient Experience Survey data of Army active duty soldiers (December 2017 through May 2018) to investigate the relationship between access to care and medical readiness. Medical readiness scores were examined a month before and a month after a medical encounter. Medical Readiness Categories (MRC) were collected from the Army Medical Operational Data System Mainframe. Respondents of the survey were matched to MRC data. Comparisons were made using chi-square tests and Wilcoxon rank-sum non-parametric tests to determine whether there were differences in readiness and patient experience ratings before and after the encounter. Logistic regressions were also conducted to predict the odds of non-readiness based on the type of health care visit.

Results: Soldiers who were medically non-ready were more likely to be above age 35 years or have specialty care encounters. Results indicated those meeting all medical readiness requirements or having minor medical issues that could be resolved quickly, generally rated access to care slightly lower compared to those who were medically non-ready. Musculoskeletal Injuries (MSKIs) are the leading cause of medical non-readiness. As a result, this study explored access to care for MSKIs. Although there were no statistical differences in access ratings for those with MSKIs compared to those without MSKIs, there were statistically significant differences in self-reported health. Individuals with MSKIs tended to report poorer health status. Those with specialty care visits had 1.79 times significantly greater odds ($p<.05$) of being non-medically ready compared to those with primary care. For visits related to MSKI (e.g., physical medicine, orthopedic, or chiropractic etc.), those with an orthopedic or occupational therapy visit had 1.25 and 1.59 significantly greater odds ($p<.05$) of being considered not medically ready compared to all other MSKI related visits before the encounter. However, after the encounter, those with orthopedic care had significantly higher odds of improved readiness.

Conclusions: Findings from this study help contextualize who is considered medically non-ready as well as differences in access to care experiences for this group. The lowest scoring areas for improving access to care include ease of making appointment, time between scheduling an appointment and the visit, and being seen past the scheduled time. Given that musculoskeletal injuries tend to require long term specialized treatments such as physical and occupational therapy, findings from the logistic regressions suggest that access and adherence to such treatments, particularly for orthopedic care, are helpful in improving medical readiness.

Keywords: military medical readiness, access to care, patient experience, musculoskeletal injuries

Background

Military readiness refers to the ability of soldiers to deploy immediately.[1] The Army defines medical readiness as a "standardized system across the total force to enable the commander to measure, achieve, and sustain soldiers' health to perform their war time requirement (military occupational specialty/area of concentration) from induction to separation."[2] If a soldier experiences health issues, it can impact their readiness status and consequently overall military readiness.

The primary foci of Department of Defense (DoD) readiness and health assurance initiatives are as follows: develop policies, monitor status of individual medical readiness, provide resources to ensure personnel are medically ready to deploy, and streamline and improve processes in military health.[3,4] This guarantees the health of soldiers is prioritized as the system evolves to optimize processes and improve readiness policy. The goal is that every soldier meets all components of the individual medical readiness (IMR) program so the DoD ensures forces are available and healthy for in-theatre operations. The DoD IMR program includes six primary elements for assessment: periodic health assessment (PHA), dental readiness (e.g., up-to-date dental examinations), readiness immunizations, readiness laboratories, individual medical equipment, and assessment of deployment limiting medical conditions.[3-5] The Army includes vision and hearing screenings as two additional IMR elements, but these are included in preventive medicine assessment by Navy and Air Force. These assessments and requirements have unique scores and classes which designate an individual soldier's levels of readiness. These aspects of readiness extend to preventive health (such as vision or hearing screenings, women's health, and cancer screenings) as well as overall physical and mental status of soldiers.

Unresolved health conditions that require frequent medical visits or limit physical activities, such as certain musculoskeletal conditions or a health problem that requires surgery and follow up rehabilitation, typically prevent the soldier from being deployed.[6] According to the Army 2018 Readiness of the Force Report, over 70% of the injuries in 2017 were micro-traumatic or cumulative musculoskeletal injuries (MSKIs) with 56% of soldiers reporting new injuries in 2017 compared to 2016.[7] MKIs were the top reason for outpatient healthcare visits for soldiers in 2012 and the third leading diagnosis for hospital admissions.[8]

MSKIs as cited previously are a key health issue preventing soldiers from deployment. MSKI disorders affect muscles, tendons, blood vessels, nerves, and other soft tissue.[9,10] MSKIs can be defined as a type of muscle or joint injury caused by repetitive trauma, including injuries such as sprains and stress fractures.[11] The most prevalent MSKIs found in military settings are situated in the lower extremities, with micro-traumas and overuse being the most likely type of MSKIs.[12] Poor physical fitness, comorbidities, and barriers in access to care are all risk factors that play an important role in the development of MSKIs.

Many assumptions are made about what factors of care delivery promote medical readiness, though few have been evaluated with a scientific approach. For instance, it is presumed that to be medically ready the soldier needs to have access to healthcare in a timely manner. In this study, we investigate the link between patient experience with access to care and individual medical readiness. Patient experience research has shown a correlation between positive experience and better health outcomes.[13] The hypothesis is that higher ratings on access to care survey measures coincide with medical readiness. Patient satisfaction surveys are one way of assessing individuals' experiences and satisfaction with access to care and the health care system in general. Evaluating this measure may provide insight into assessing how medical readiness is affected by access to care. The role of access is multidimensional and instrumental in impacting patient health outcomes. Many factors such as appointment availability and ease of making appointments affect perception of care. Long wait times to see a provider are significantly associated with lower patient experience ratings.[14] This is also true in the military healthcare setting where analyses have shown medical treatment facility (MTF) clinic availability and wait times are significantly correlated with overall patient experience.[15,16] Understanding limitations in access to healthcare can inform MTF commanders and staff on areas for improvement such as scheduling, increasing the availability of preventive visits, and decreasing wait times. Patient experience surveys help provide additional context on what soldiers encounter while navigating the healthcare system and insights on access to care issues that may impact medical readiness. Given that musculoskeletal issues are the top reason for non-deployment, this study also explores differences in access to care ratings between those with MSKIs and those without MSKIs among a subset of soldiers.

Sample & Methodology

The Joint Outpatient Experience Survey (JOES) measures patient experiences and satisfaction at all MTFs (consisting of over 50 hospitals and 400 clinics) across the services and provides insight about beneficiary healthcare experiences with the goal of improving patient care in the Military Health System (MHS). This study uses data from JOES that covers medical encounters from

Table 1. Soldier Time 1 and Time 2 sample characteristics by medical readiness category (MRC).

Characteristics	Time 1 MRC1 & 2 (n = 13,753, 82.24%)	Time 2 MRC1 & 2 (n = 13,280, 79.28%)	Time 1 MRC3 & 4 (n = 2,971, 17.76%)	Time 2 MRC3 & 4 (n = 3,469, 20.71%)
	No. (%)	No. (%)	No. (%)	No. (%)
Gender				
Female	3,112 (22.63)*	3,002 (22.61)*	919 (30.93)*	1,037 (29.89)*
Male	10,641 (77.37)*	10,278 (77.39)*	2,052 (69.07)*	2,432 (70.11)*
Age Groups				
18-24	1,423 (10.35)*	1,377 (10.37)*	398 (13.4)*	473 (13.64)*
25-34	4,950 (35.99)*	4,734 (35.65)*	988 (33.25)*	1,207 (34.79)*
35-44	5,020 (36.50)*	4,863 (36.62)*	998 (33.59)*	1,155 (33.29)*
45+	2,360 (17.16)*	2,306 (17.36)*	587 (19.76)*	634 (18.28)*
Care Type				
Primary Care	6,339 (46.09)*	6,112 (46.02)*	960 (32.31)*	1,211 (34.91)*
Specialty Care	7,414 (53.91)*	7,168 (53.98)*	2,011 (67.69)*	2,258 (65.09)*
Health Status				
Excellent	4,018 (30.54)*	3,972 (31.23)*	617 (21.66)*	676 (20.44)*
Very Good	4,822 (36.65)*	4,688 (36.86)*	846 (29.69)*	986 (29.81)*
Good	3,391 (25.78)*	3,209 (25.23)*	874 (30.68)*	1,061 (32.07)*
Fair/Poor	925 (7.03)*	851 (6.69)*	512 (17.97)*	585 (17.68)*
Change in Readiness	*Lower Readiness T2*	*Same Readiness T1 & T2*	*Higher Readiness T2*	
	2,730 (16.34)	11,124 (66.59)	2,852 (17.07)	

*p<.001 based on chi-square tests. Note. Readiness Time 1 is one month before JOES encounter and Readiness Time 2 is one month after the JOES encounter. Some individuals may be missing a readiness score either at Time 1 or Time 2.

December 2017 to May 2018 for select Army MTFs and applies medical readiness categories (MRC) collected from the Army Medical Operational Data System Mainframe. The study matched JOES respondents to MRC data within the system. The study was approved by an Institutional Review Board.

Survey measures on access to care and general patient satisfaction and experience considered in this analysis are summarized below.

Access to care questions on the survey:

1) The ease of making the appointment (Poor, Fair, Good, Very Good, Excellent).

2) The amount of time between when you made the appointment until your actual visit (Poor, Fair, Good, Very Good, Excellent).

3) If seen past your scheduled appointment time, the effort made to keep you informed about the delay (Poor, Fair, Good, Very Good, Excellent).

4) In general, I am able to see my provider when needed (Strongly Disagree, Somewhat Disagree, Neither Agree nor Disagree, Somewhat Agree, Strongly Agree).

Patient satisfaction and experience questions:

5) Overall, how satisfied are you with your visit with this provider? (Completely Dissatisfied, Somewhat Dissatisfied, Neither Satisfied nor Dissatisfied, Somewhat Satisfied, Completely Satisfied).

6) Overall, I am satisfied with the healthcare I received on this visit (Strongly Disagree, Somewhat Disagree, Neither Agree nor Disagree, Somewhat Agree, Strongly Agree).

7) In general, my provider team considers my values and opinions when we make decisions about my healthcare (Strongly Disagree, Somewhat Disagree, Neither Agree nor Disagree, Somewhat Agree, Strongly Agree).

8) In general, how would you rate your overall health? (Poor, Fair, Good, Very Good, Excellent).

The study examined readiness scores before (referred to as Time 1) and after (referred to as Time 2) a medical encounter for which a respondent completed the JOES survey. Comparisons were made to determine whether there were differences in readiness or patient experience ratings before or after the surveyed encounter. The Army definition of the medical readiness categories[17] (MRC) (or the readiness score) are as follows:

- MRC1 = Deployable, meets all requirements.
- MRC2 = Deployable, requirements can be resolved with in 72 hours.
- MRC3 = Non-deployable, medically non-ready.
- MRC4 = Disqualification/status unknown.

Chi square tests determined differences in soldier characteristics for MRC1\MRC2 compared to MRC3/MRC4 separately for Time 1 and Time 2. Wilcoxon rank-sum non-parametric tests tested for equality of distributions of the survey access measures for MRC1\MRC2 compared to MRC3/MRC4 at Time 1 and Time 2. Additional comparisons and logistic regressions explored links between access to care and medical readiness as they relate to MSKIs for subsets of soldiers. Specifically, differences by MSKI status, MRC category, and visit type associated with MSKIs were included in these analyses.

Results

Sample Characteristics: Most soldiers are in MRC1/

MRC2 (Table 1). This is consistent both at Time 1 and Time 2 (82.2% and 79.3% respectively). Regarding change in readiness score, 66.6% of soldiers did not experience a change in score while 16.3% experienced a lower readiness score at Time 2. The Army active duty sample is majority male and between the ages of 25 and 44. MRC3/MRC4 has a greater proportion of those 45 and older compared to MRC1/MRC2. Those with MRC1/MRC2 are more likely to have a primary care visit and excellent/very good health, while those with MRC3/MRC4 are more likely to have a specialty care visit and report fair/poor health. More than half of those with MRC3/MRC4 had a specialty care visit. These characteristics significantly distinguish those who are deployable to those who are considered non-deployable (p<.001). These demographic and care trends are consistent at Time 2.

Table 2. Ratings in Time 1 and Time 2 by medical readiness category (MRC).

Measure	Time 1	Time 2	Time 1	Time 2
	MRC1&2 (n = 13,753, 82.24%)	MRC1&2 (n = 13,280, 79.28%)	MRC3&4 (n = 2,971, 17.76%)	MRC3&4 (n = 3,469, 20.71%)
Ease of Making Appointment (%)				
Excellent	53.32*	53.77	56.83*	54.69
Very Good to Poor	46.68*	46.23	43.17*	45.31
Time Between Scheduling And Visit (%)				
Excellent	48.77	48.69	48.50	48.70
Very Good to Poor	51.23	51.31	51.50	51.30
Seen Past Scheduled Time (%)				
Excellent	48.01*	48.89	51.68*	48.42
Very Good to Poor	51.99*	51.11	48.32*	51.58
Satisfaction with Healthcare (%)				
Strongly Agree	81.38	81.65	81.71	80.45
Somewhat Agree to Strongly Disagree	18.62	18.35	18.29	19.55
See Provider When Needed (%)				
Strongly Agree	62.81	63.23*	62.96	61.37*
Somewhat Agree to Strongly Disagree	37.19	36.77*	37.04	38.63*
Team Values Opinions (%)				
Strongly Agree	72.07	72.33	72.88	71.67
Somewhat Agree to Strongly Disagree	27.93	27.67	27.12	28.33

*Significant differences (p<0.05) based on Wilcoxon rank-sum non-parametric test on 5-point Likert scare variable.

Readiness & Patient Experience with Access to Care—Differences by MRC: Table 2 shows proportions reporting top-box scores (i.e., "Excellent," "Strongly Agree," or "Completely Satisfied") for access and satisfaction measures and corresponding MRC groups for Time 1 and Time 2. There are significant differences (p<0.05) between ratings of Ease of Making Appointment, with those in MRC3/MRC4 rating the top-box score ("Excellent") nearly 4 points higher compared to those in MRC1/MRC2 at Time 1. There are also significant differences (p<0.05) between ratings of Seen Past Scheduled Time with those in MRC3/MRC4 rating the top-box score higher compared to those in MRC1/MRC2 at Time 1. Finally, there are significant differences (p<0.05) at Time 2 where the MRC1/MRC2 group rated See Provider When Needed top-box slightly higher compared to the MRC3/MRC4 group. Apart from these significant measures, the MRC1/MRC2 and MRC3/MRC4 groups generally rated survey measures similarly.

Readiness & MSKIs—Differences by MSKI Status: Analyses explore the link between access to care and medical readiness as they relate to MSKIs on a subset of the sample (n=1,367) based on data availability. Over a third of the sample (36% or 491) have MSKIs. Those with MSKIs tended to rate ease of making appointments and availability to see provider comparably to those without MSKIs (Table 3). However, those with MSKIs were more likely to report worse self-reported health status compared to those without MSKIs.

A further look into MSKI condition and MRC status shows that soldiers with MSKIs and in MRC3/MRC4 were more likely to rate ease of making appointment and ability to see provider when needed "Excellent" compared to those in MRC1/MRC2. Finally, soldiers with MSKIs in MRC3/MRC4 reported significantly worse health status than those in MRC1/MRC2.

Table 3. Patient experience access to care and health status ratings by muskuloskeletal injury (MSKI) and medical readiness category (MRC).

Measure	MSKI Status		MSKI Present+	
	MSKI Not Present (n = 876)	MSKI Present (n = 491)	MRC 1&2 (n = 285)	MRC 3&4 (n = 206)
Ease of Making Appointment (%)				
Excellent	55.7	53.7	50.0	60.3
Very Good	26.1	25.5	30.8	23.3
Good	12.3	11.8	10.7	8.2
Fair	3.6	6.1	5.1	4.1
Poor	2.4	2.9	3.4	4.1
See Provider When Needed (%)				
Strongly Agree	65.3	65.1	64.8	69.7
Somewhat Agree	17.8	18.7	20.1	10.1
Neither Agree nor Disagree	11.2	8.3	9.2	7.9
Somewhat Disagree	3.0	4.6	2.9	9.0
Strongly Disagree	2.7	3.3	2.9	3.4
Health Status (%)				
Excellent	33.8*	15.4*	14.2*	4.5*
Very Good	42.4*	33.4*	38.0*	21.3*
Good	19.4*	35.9*	38.3*	48.3*
Fair	4.1*	11.8*	7.7*	16.9*
Poor	0.3*	3.5*	1.8*	9.0*

*Significant differences based on Wilcoxon rank-sum non-parametric test.
+ Only pertains to the 491 with MSKI condition present.

Predicting Non-readiness & Change in Readiness: The analysis here examines the impact of an MSKI encounter on predicting medical readiness. Logistic regression analyses help determine whether MSKI related visits predict medically non-ready (MRC3/MRC4) classification before and after the surveyed encounter. Most of the visits (54%) were in physical therapy (Table 4). These MSKI visit codes

Table 4. Distribution and odds of medical readiness category (MRC) MRC3/MRC4 by musculoskeletal injury (MSKI) related visits before and after a medical visit.

MSKI Visit	Freq	Percent	MRC3/MRC4 Time 1 Odds Ratio	MRC3/MRC4 Time 2 Odds Ratio	Lower Readiness Time 2 Odds Ratio	No Change Time 1 & Time 2 Odds Ratio	Higher Readiness Time 2 Odds Ratio
Physical Medicine	317	9.47	0.89 (0.67-1.19)	0.76 (0.57-1.01)	0.84 (0.56-1.25)	1.57 (1.16-2.12)*	0.58 (0.39-0.85)*
Orthopedic	612	18.28	1.25 (1.01-1.55)*	1.32 (1.07-1.62)*	0.98 (0.73-1.32)	0.81 (0.65-1.00)*	1.36 (1.07-1.74)*
Chiropractic	284	8.48	0.41 (0.29-0.58)*	0.43 (0.31-0.60)*	0.72 (0.47-1.10)	1.60 (1.18-2.17)*	0.64 (0.44-0.94)*
Podiatry	143	4.27	0.98 (0.63-1.52)	1.15 (0.76-1.74)	1.23 (0.71-2.12)	0.76 (0.50-1.15)	1.25 (0.77-2.02)
Physical Therapy	1,795	53.61	1.05 (0.89-1.24)	1.11 (0.94-1.30)	1.10 (0.88-1.37)	0.90 (0.77-1.06)	1.08 (0.89-1.31)
Occupational Therapy	197	5.88	1.59 (1.14-2.21)*	1.27 (0.91-1.76)	1.19 (0.76-1.85)	0.91 (0.65-1.27)	1.00 (0.66-1.51)
Specialty Care+	12,082	58.47	1.79 (1.65-1.95)*	1.59 (1.47-1.72)*	1.02 (0.94-1.11)	1.11 (1.04-1.19)*	0.83 (0.77-0.90)

**Statistically significant where p<.05.*
+ Primary Care was the reference category for Specialty Care.
95% Confidence intervals are presented in parentheses. Each MSKI related visit, except for Specialty Care, was compared to all other MSKI related visits (e.g., physical medicine was a dichotomous variable where all other MSKI related visits would be included as the reference category for physical medicine).

make up 16% of all possible visit codes in the sample including those not related to MSKIs. Podiatry visits make up the fewest number of visits in the sample. Table 4 also includes odds ratios, or the odds of being non-medically ready (MRC3/MRC4) compared to medically ready (MRC1/MRC2). Those with orthopedic and specialty care visits had increased odds of being in MRC3/MRC4 both at Time 1 and Time 2. At Time 2, the odds of occupational therapy visits being associated with MRC3/MRC4 was not significant. Those with physical medicine and chiropractic visits had decreased odds at Time 1 and Time 2 of being non-medically ready as well as podiatry visits, although this only occurred at Time 1. Additional logistic regressions yielded the odds of changing readiness status between Time 1 and Time 2 based on the type of MSKI related visit a patient had. Those with orthopedic visits had increased odds of improved readiness status in Time 2.

Discussion

Given the relative lack of studies evaluating what factors affect medical readiness, and the fact this study contradicts a common assumption that better perceived access to care coincides with medical readiness, this study highlights the need for further evaluation regarding current and future assumptions of promoting medical readiness. Findings from this study help contextualize who is considered not medically ready as well as differences in patient experience for this group. Results indicated gender, older age, specialty care type, and lower self-reported health status were distinguishing characteristics between MRC1/MRC2 and MRC3/MRC4 active duty soldiers receiving care at US Army MTFs. MRC3/MRC4 soldiers were more likely to be above the age of 35, male, or have a specialty care encounter. This finding corresponds with military findings—over time soldiers are more likely to experience morbidities and injuries because of length of time in service and aging.[18,19] It is likely increased morbidity coincides with an increase in specialty care visits. As a result, improved access to specialty care providers is key for older, active duty service members.

Most of the study sample were in MRC1/MRC2 or considered deployable after addressing minor health requirements to be fully medically ready. Interestingly, soldiers in MRC1/MRC2 were more likely to rate access to care measures related to scheduling and being seen in a timely manner lower compared to MRC3/MRC4 soldiers. This finding was counter to our initial hypothesis that higher patient experience scores would correspond with increased medical readiness. This study highlights those who are receiving certain types of care have increased odds of transitioning to MRC1/MRC2 sooner. Given the 72-hour rule in meeting the readiness requirement, timely and adequate access to care is particularly critical for soldiers in MRC1/MRC2.

Access to care can encapsulate accessibility to specialty care appointments, wait times, and ease of scheduling appointments. Readiness has a time sensitive aspect, so being able to easily schedule appointments in a timely manner is essential to ensuring soldiers are "fit for duty," thus soldiers in MRC1/MRC2 have a greater push to obtain care quickly. Being able to obtain and schedule appointments, as well as taking wait time into consideration is especially compounded with soldiers who must consider work and training schedules.[18] Loss of duty time to access medical care impacts the mission of the soldier's unit. At some MTFs, there is a disconnect between the appointment structure and schedules of soldiers that creates a barrier to access, a sentiment that is often heard in the comments of soldiers unable to schedule appointments into their work hours.[20] Specialty care appointments that may be more relevant for those in MRC3/MRC4, as referrals are often needed, may result in additional delays. Access to care standards in MTFs specify primary care must be available within 7 days and specialty care within 28 days;[21] however, there is variability in how these standards are met across MTFs.

To improve access and perceptions regarding access for active duty personnel, the MHS is implementing changes to reduce the complications with scheduling and wait times. Changes in booking protocols that will allow primary care clinics to book into specialty care clinics before the soldier leaves the MTF will have a significant impact on returning the soldier to duty quickly. Additionally, the MHS monitors total number of primary[22] and specialty care[23] appointments booked and average number of days to appointment for active duty. Other considerations such as utilizing advanced access scheduling protocols will allow patients to schedule same day or next day appointments, reducing wait times and increasing access.[24] Ensuring confidence in patients' perception in their access means they are more likely to utilize care and preventive services, which leads to better health outcomes and reduced complications.[25]

Transportation and physical accessibility of facilities can also impede access to care. Transportation barriers lead to missed appointments and delayed care, which in turn, lead to poorer management of illness and poorer health outcomes.[26] If distance to the MTF from duty location is far, access to healthcare becomes significantly diminished. It is known in rural communities, for example, distance to medical facilities can be a barrier for veterans in seeking healthcare.[27] Additionally, a study on access to behavioral healthcare for geographically remote active duty soldiers found remoteness (more than a 30-minute drive) linked with disproportionately lower use of specialty behavioral health care services.[28] Remote or rural environments result in several barriers when trying to access care, including travel distance, transportation problems, and difficulty taking time off to attend appointments.[29] Given the importance of access to healthcare in ensuring medical readiness, facilities with barriers to access may result in soldiers not obtaining care (i.e., long wait times, canceled appointments, lack of parking, facilities too far away, etc.). This affects health as well as the willingness of soldiers to seek out treatment or return for follow up appointments.

Comparison of gender differences in the study sample indicated there were more female soldiers in MRC3/MRC4 compared to MRC1/MRC2, and this was also true by MSKI status. A study predicting medical non-readiness among US Army soldiers also found female recruits were more likely to not be medically ready compared to males.[18] In a different study, researchers investigating the epidemiology of MSKIs among soldiers found stress fractures were significantly more prevalent among female recruits compared to males. Overuse injuries and back pain were also cited as major issues for female recruits.[30] Although females comprise a lower proportion of the active duty population in this study, additional research on the risks and pattern of MSKI related to non-readiness should be a focus of this group.

Those with MSKIs were more likely to report lower health status compared to those without MSKIs. Furthermore, logistic regression analyses using MSKI related visits found orthopedic and occupational health visits predicted an increase in the odds of not meeting medical readiness requirements. However, in Time 2 those with orthopedic visits had increased odds of improving their readiness status (e.g., moving from MRC 3 to MRC 2). Given that musculoskeletal injuries tend to require long term specialized treatments, findings from the logistic regressions suggest access and adherence to such treatments, particularly for orthopedic care, are helpful in improving medical readiness. Soldiers with MSKI related visits in the MRC 3/MRC 4 categories have a higher acuity and need for access. When they obtain access to orthopedic care, we see improvement to MRC1/MRC2.

Military medical readiness is a key priority for the US DoD; therefore, additional studies, to include the other Services (i.e., Navy, Air Force), must be conducted to better understand the link between soldier experience with their healthcare and improving their health outcomes. Timely care is crucial to meet health, wellness, and prevention goals, and to ensure all service members are fit for duty. The medical system needs to understand and focus additional efforts in supporting and strengthening the medical readiness of the soldier to benefit the mission.

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Authors

Beatrice Abiero is with Ipsos US Public Affairs, Washington DC.

Melissa Gliner is with Defense Health Agency, Falls Church VA.

Sharon Beamer is with US Navy, Bureau of Medicine and Surgery, Falls Church VA.

Amanda Sackett is with Ipsos US Public Affairs, Washington DC.

Kimberley Marshall-Aiyelawo is with Defense Health Agency, Falls Church VA.

Janice Ellison is with Air Force Medical Readiness Agency, Joint Base San Antonio-Lackland, San Antonio TX.

Terry McDavid is with US Army, Office of the Surgeon General, Falls Church VA.

John de Geus is with US Navy, Bureau of Medicine and Surgery, Falls Church VA.

Humerus Intraosseous and Intravenous Administration of Epinephrine in Normovolemic and Hypovolemic Cardiac Arrest Porcine Models

COL Denise Beaumont, CRNA, DNAP
LTC Michelle Johnson, CRNA, DNP
Julie G. Hensler, PhD
Dawn Blouin, BS
Joseph O'Sullivan, CRNA, PhD
Don Johnson, PhD

Abstract

Objective: The aim of this study was to compare area under the curve (AUC), frequency, and odds of return of spontaneous circulation (ROSC) when epinephrine was administered in hypovolemic and normovolemic cardiac arrest models.

Methods: Twenty-eight adult swine were randomly assigned to 4 groups: HIO Normovolemia Group (HIONG); HIO Hypovolemia Group (HIOHG); IV Normovolemia (IVNG); and IV Hypovolemia Group (IVHG). Swine were anesthetized. The HIOH and IVH subjects were exsanguinated 35% of their blood volume. Each was placed into arrest. After 2 minutes, cardiopulmonary resuscitation was initiated. After another 2 minutes, 1 mg of epinephrine was given by IV or HIO routes; blood samples were collected over 5 minutes and analyzed by high-performance liquid chromatography. Subjects were defibrillated every 2 minutes.

Results: The AUC in the HIOHG was significantly less than both the HIONG ($p = 0.047$) and IVHG ($p = 0.021$). There were no other significant differences in the groups relative to AUC ($p > 0.05$). HIONG had a significantly higher occurrence of ROSC compared to HIOHG ($p = 0.018$) and IVH ($p = 0.018$) but no other significant differences ($p > 0.05$). The odds of ROSC were 19.2 times greater for HIONG compared to the HIOHG.

Conclusion: The study strongly supports the effectiveness of HIO administration of epinephrine and should be considered as a first-line intervention for patients in cardiac arrest related to normovolemic causes. However, our findings do not support using HIO access for epinephrine administration for patients in cardiac arrest related to hypovolemic reasons.

Keywords: intraosseous; shock; epinephrine, area under the curve

Background

Approximately 550,000 cardiac arrests occur each year just in the US.[1] Cardiac arrest can be classified as either hypovolemic or normovolemic causes.[2] Hemorrhage is the leading cause of cardiac arrest from trauma in both civilian and military sectors.[3-8] Mortality from hemorrhage approaches 2 million worldwide. Hemorrhage can lead to hypovolemic shock and subsequent cardiac arrest.[1] Cardiovascular disease is the leading cause of arrest in a normovolemic scenario. Other normovolemic causes of arrest include myocardial infarct, blunt trauma, drowning, and electrocution.[9-14]

Regardless of cause, studies have demonstrated time to epinephrine administration for any patient in arrest is essential for survivability.[15-17] For every minute of delay, chances of survival are decreased by 9%.[18] Therefore, vascular access is essential in increasing the chances of survival and can be delayed in attempting intravenous

(IV) access. In a cardiac arrest situation, the victim's veins have collapsed, particularly in hypovolemic shock, making IV access difficult and very time consuming even for the most skilled clinician.

The American Heart Association (AHA) recommends for victims in arrest 1 mg epinephrine should be administered with repeated dosing every 3-5 minutes.[19] Further, AHA recommends the establishment of intraosseous needle (IO) access if IV access is not rapidly obtained.[19] Several studies demonstrated the IO and IV have similar efficacy.[20-29] However, most IO studies have investigated drugs used in a normovolemic model. We speculated there may be differences in patients with hypovolemia because of the release of endogenous epinephrine. Both endogenous and the exogenous administered catecholamines may have an additive effect causing vasoconstriction to the bones. Subsequently, there may be less delivery of epinephrine from the bone into the systemic circulation.[30] In fact, Voelckel et al found that hemorrhage along with epinephrine administration reduces flow to the bones to almost zero.[31] Area under the curve (AUC) reflects the body's exposure to epinephrine after administration. Epinephrine administration in a hypovolemic compared to a normovolemic model may change the volume of distribution. Subsequently, this reduces AUC that may translate into less frequency of return of spontaneous circulation (ROSC). Few studies have investigated the effects of hypovolemia on the efficacy of intraosseous epinephrine administration in a cardiac arrest scenario. In separate studies, Neill and Yauger found HIO and tibial intraosseous (TIO) were ineffective in achieving ROSC in a pediatric cardiac arrest hypovolemic model.[32,33] Only one study compared the effects of IO epinephrine administration using hypovolemia and normovolemia in adult subjects.[2] In that study, Long determined the humerus intraosseous (HIO) administration of epinephrine was very effective in a normovolemic model but not in a hypovolemic model, but they did not investigate the effects of AUC.[2]

There are no studies comparing HIO and IV administration of epinephrine relative to AUC in hypovolemic and normovolemic cardiac arrest models. The findings of this study give direction for making decisions regarding vascular access for patients in cardiac arrest; hence, it has the potential of saving lives. The aims of this study were to compare AUC, frequency, and odds of ROSC when epinephrine was administered by HIO and IV routes in hypovolemic and normovolemic models of cardiac arrest.

Methods

This study was funded by a TriService Research Program Grant and approved by the Institutional Animal Care and Use Committee (Naval Medical Research Unit). The study was conducted at the Navy Triservice Medical Research Center in San Antonio, TX. To avoid as much variability as possible, we purchased swine from the same vendor. All subjects were cared for according to the Animal Welfare Act and the Guide for the Use of Laboratory Animals.[34] This study consisted of 4 groups (N=28) of adult male Yorkshire-cross, sus scrofa, swine. By using a random number generator, we assigned 7 swine to each of 4 groups: HIO Normovolemic Group (HIONG); HIO Hypovolemic Group (HIOHG); IV Normovolemic Group (IVNG) and IV Hypovolemic Group (IVHG). Male pigs were used to avert possible effects from the female hormones. The swine weighed ~70 kg which approximates the average weight of an adult, male human.[35,36] The rationale for using pigs was because the cardiovascular, pulmonary, and bone physiology are very similar to humans.[37,38] Each of the swine received a thorough health examination to confirm they were in good health on arrival and before the study. After midnight on the day before the experiment, the subjects were not allowed food but allowed to drink water up until induction of anesthesia. For subjects in the HIO groups, we inserted the EZ-IO device, and after insertion, we aspirated blood and/or bone marrow to make certain the device was in the humerus.

An intramuscular injection of Telazol (4.4 mg/kg) and then anesthesia (1 to 2 % isoflurane) were administered. The hypovolemic groups were exsanguinated 35% of their blood volume to represent a Class III hemorrhage. For all subjects, an electric current was sent through each of the swine's heart to produce cardiac arrest, a procedure developed by the investigators.[39] Anesthesia was discontinued, and each animal was left in arrest for 2 minutes. The rationale for 2 minutes was this was the minimum amount of time to detect cardiac arrest. Mechanical chest compressions at 100 per minute were initiated using a mechanical compression device. The rationale for using the device was to maintain consistency and reproducibility. Ventilation rates of 8 to 10 per minute were used. After another 2 minutes, 1 mg epinephrine was given by IV or HIO routes; blood samples were then collected over 5 minutes.

Serum concentration of epinephrine was determined by using high-performance liquid chromatography (HPLC), the industry standard. The individual performing the calculations was blinded to group assignment. Defibrillation was administered every 2 minutes as recommended by AHA.[19] The hypovolemic groups received 500 mL of 5% albumin following blood sampling. Cardiopulmonary resuscitation (CPR) continued

Figure 1. Group comparison of area under the curve.

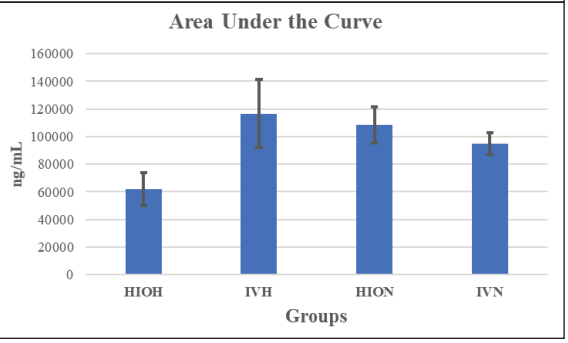
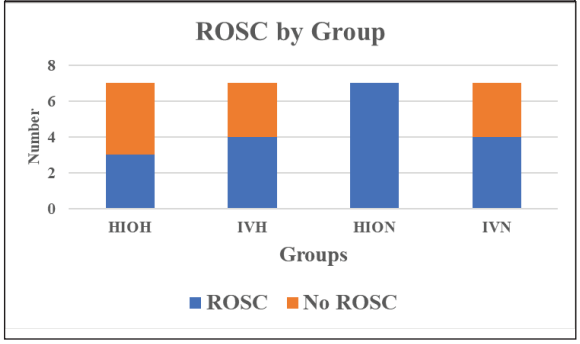


Figure 2. Return of spontaneous circulation by group.



until ROSC. If ROSC was not achieved, the investigators implemented resuscitation efforts for ROSC for 20 minutes. Once ROSC was achieved, subjects were monitored for 30 minutes. ROSC was operationally defined as a mean arterial pressure of at least 60 mmHg and a palpable pulse.

Investigators calculated a large effect size of 0.6 based on previous, similar research.[40-42] Using an α of 0.05, a large effect size of 0.6, and a power of 0.8, calculations determined the needed sample size of 28 (n=7 per group). Power analysis was performed using standard software. Means and standard error of the means were calculated for each group. A multivariate analyses of variance (MANOVA) was used to determine if there were any significant differences in the pretest data including weight, cardiac output, stroke volume, systolic blood pressure, mean arterial blood pressure, temperature, heart rate, total blood volume, and the amount of blood exsanguinated in the hypovolemic groups. A univariate ANOVA was used to determine if there were significant differences in the AUC by group. A Chi-Square was used to determine if there were significant differences in frequency of ROSC by group. All statistics were calculated using standard software. Odds of ROSC by group were calculated by using an odds ratio calculator.

One of the major limitations of this study was a small sample size. Nevertheless, investigators had enough power to find significance. Another limitation was not all the investigators were blinded to group assignment; although, they rigorously adhered to the procedures of this study. Also, the findings of this study may not be generalizable to humans; however, the cardiovascular, bone, and respiratory systems of the models are very similar to humans.[37,38]

Results

A MANOVA indicated no significant differences in the pretest data indicating the groups were equivalent on these variables ($p>0.05$). A univariate ANOVA indicated significant differences in the AUC by group. The AUC in the HIOHG was significantly less than both the HIONG ($p=0.047$) and IVHG ($p=0.021$). There were no other significant differences in the groups relative to AUC ($p>0.05$). (Figure 1). A Chi-Square indicated that the HIONG had a significantly higher occurrence of ROSC compared to HIOHG ($p=0.018$) and IVH ($p=0.018$) but no other significant differences ($p>0.05$) (Figure 2) The odds of ROSC were 19.2 times greater for HIONG compared to the HIOHG.

Discussion

The AUC in the HIOHG was significantly less compared to both the HIONG and IVHG, and the frequency of ROSC was significantly higher in the HION compared to both the HIOHG and IVHG. The odds of ROSC were greater for the HIONG compared to the HIOHG. Following acute blood loss, activation the sympathetic nervous system and increased release of endogenous catecholamines serve to shunt blood away from peripheral tissues such as bone, which are not necessary for survival.[43,44] Thus, humeral bone marrow may be less perfused in hypovolemic subjects than in normovolemic subjects. Consistent with this idea, studies show maximum plasma concentration (Cmax) is lower, and time to maximum plasma concentration (Tmax) is delayed following HIO epinephrine administration in hypovolemic compared to normovolemic subjects.[2] Our data are in agreement with previous work and suggest that in hypovolemic subjects, plasma concentrations of epinephrine following HIO administration were insufficient for ROSC in the majority of subjects. By contrast, plasma concentration of epinephrine following HIO administration in normovolemic subjects were sufficient for all subjects to achieve ROSC.[2]

Early administration of epinephrine is essential for ROSC for patients in cardiac arrest. Valuable time can be saved by using the HIO route compared to the IV route.

Early administration of epinephrine is associated with a higher probability of ROSC in patients with cardiac arrest and can significantly reduce odds of death by 58% if administered within 5 minutes.[45,46] In this study, it took less than 10 seconds to insert the EZ-IO device. Major advantages of using the IO device are the rapid vascular access, and CPR does not have to be interrupted compared to IV insertion. Also, IV access can be difficult and very time consuming. Intravenous failure rates have shown to be from 10 to 40% in patients not in arrest. The time to obtain IV access is greatly varied from 2.5 to 16 minutes to as long as 55 minutes in critically ill patients. which might be longer in a patient in cardiac arrest.[45,46] In summary, the present study strongly supports the effectiveness of HIO administration of epinephrine and should be considered as a first-line intervention for patients in cardiac arrest related to normovolemic causes. However, our findings do not support using HIO access for epinephrine administration for patients in cardiac arrest from related to hypovolemic reasons.

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Authors

COL Denise Beaumont serves as Director, United States Army Graduate Program, San Antonio, TX.

LTC Michelle Johnson is Former Executive Officer, United States Army Graduate Program in Anesthesia Nursing, San Antonio, TX.

Julie G. Hensler serves as Professor, United States Army Graduate Program in Anesthesia Nursing, San Antonio, TX.

Dawn Blouin serves as Research Assistant, United States Army Graduate Program in Anesthesia Nursing, San Antonio, TX.

Joseph O'Sullivan is a retired US Army lieutenant colonel.

Don Johnson serves as Professor and Director of Research, United States Army Graduate Program in Anesthesia Nursing, San Antonio, TX.

A Retrospective, Epidemiological Review of Type 2 Diabetes Mellitus in a Military Population

Tyler L. Collette, PhD
MAJ Jason L. Judkins, PhD, DSc
MAJ Morgan Gettle
Brian A. Moore, PhD
MAJ Michelle Lee, MD
MAJ Darrick Beckman, MD
Mari-Amanda Dyal, PhD
2LT Ashton Rouska, BA
MAJ Joshua Tate, MD
Jana L. Wardian, PhD, MSW

Abstract

Objective: Examine incidence rates of Type 2 Diabetes Mellitus (T2DM) in a military population over a ten-year period and whether demographic characteristics differ within the same population.

Methods: Diagnostic data and demographic variables from 23,821 active duty service members between 2006 and 2015 were analyzed from the Defense Medical Epidemiological Database.

Results: The incidence rates of new onset cases ranged from .22 (per 1,000 service members) in 2015 to a high of 1.46 (per 1,000 service members) in 2006 for T2DM without complications and .00 (per 1,000 service members) in 2007 to a high of .29 (per 1,000 service members) in 2015 for T2DM with complications. The one-sample chi-square test showed the observed, and expected frequencies differed significantly for all demographic variables tested.

Conclusions: Although there was a significant increase in the diagnosis of T2DM with complications in 2015, the overall downtrend is similar to that of the general US population. Older age and higher rank were more likely to be associated with the diagnosis of T2DM with and without complications, again suggestive of similar trends with the general US population. Continued efforts towards early diagnosis and treatment of these service members are needed to address this problem regarding military readiness.

Keywords: type 2 diabetes mellitus; active duty military; incidence rates

Introduction

Prevalence of Type 2 Diabetes Mellitus (T2DM) has increased worldwide, affecting more than 451 million people.[1] The prevalence rate within the US general population was 9.4%.[2] In contrast, from 2006-2010, the estimated prevalence of diabetes within the military was 3%.[3] The National Diabetes Statistics Report also estimated 1.5 million (6.7 cases per 1,000 persons) new cases of adult diabetes in 2015. Previous research has reported lower comparable incidence rates of T2DM in the military. A report from the Army Medical Surveillance Activity using the Defense Medical Surveillance System found incidence rates were 1.99 (Navy), 1.82 (Air Force), 1.67 (Army), and 0.56 (Marines) per 1,000 person-years.[4] Another report using the Defense Medical Surveillance System reviewed the incidence of diabetes in the military from 2008-2015 to be less than 1% overall with an incidence rate of 0.96 (Army), 0.87 (Navy), 0.58 (Air Force), and 0.20 (Marines) per 1,000 person-years for T2DM.[5]

The diagnosis of T2DM presents a unique readiness challenge to the US military as they are involved in global operations to austere environments with limited access to medical facilities. Readiness means the ability of military forces to fight and meet the demands of assigned missions.[6] Those in the US military need to maintain optimal physical readiness and be ready to deploy anywhere in the world at any time.[7]

Previous literature has shown that military forces have deployed with T2DM. As demonstrated in a recent analysis, 366 service members with T2DM were safely

deployed from 2004 to 2014.[8] From baseline to after deployment, overall glycated hemoglobin (A1C) improved slightly (6.7% to 6.5%), and body mass index demonstrated a statistically significant decline from 28.3 kg/m2 to 27.7 kg/m2 ($p < 0.0001$). Service members deploying with T2DM may create potential logistical challenges to the US Armed Forces, along with an increased financial strain on an already limited budget. Per a Congressional Budget Office report from 2014, the Department of Defense (DoD) spent $52 billion on health care or 10% of the overall DoD budget. Over a 12-year period (2000-2012), DoD spending on healthcare and healthcare-related costs had increased by 130%.[9]

Table 1. Demographics for active duty service members with type 2 diabetes with and without complications.

Table 1
Demographics for Active Duty Service Members with Type 2 Diabetes With and Without Complications

Demographic	Without Complications	Observed vs. Expected	With Complications	Observed vs. Expected
Total (*N*=23,821)	**19,064**		**4,757**	
Gender*	***n(%)***		***n(%)***	
Male [a]	16,586 (87.0%)	2.0% (1.02)	4,207 (88.4%)	4.0% (1.04)
Female [b]	2,479 (13.0%)	-13.0% (0.87)	550 (11.6%)	-13.0% (0.77)
Age at Diagnosis (Categories)*				
< 20 [b]	218 (1.1%)	-81.0% (0.19)	78 (1.6%)	-73.0% (0.27)
20-24 [b]	1,574 (8.3%)	-74.0% (0.26)	430 (9.0%)	-72.0% (0.28)
25-29 [b]	2,087 (10.9%)	-54.0% (0.46)	510 (10.7%)	-55.0% (0.45)
30-34 [b]	2,345 (12.3%)	-23.0% (0.77)	546 (11.5%)	-28.0% (0.72)
35-39 [a]	4,027 (21.1%)	92.0% (1.92)	1,000 (21.0%)	91.0% (1.91)
≥40 [a]	8,813 (46.2%)	320.0% (4.20)	2,193 (46.1%)	391.0% (4.91)
Marital Status*				
Married [a]	14,546 (76.3%)	27.0% (1.27)	3,550 (74.6%)	24.0% (1.24)
Other [b]	4,519 (23.7%)	-41.0% (0.59)	1,207 (25.4%)	-37.0% (0.63)
Race/Ethnicity*				
White [b]	9,250 (48.3%)	-19.0% (0.81)	2,119 (44.5%)	-26.0% (0.74)
Black [a]	6,138 (32.2%)	90% (1.90)	1,868 (39.2%)	131.0% (2.31)
Other [b]	3,677(19.3%)	-16.0% (0.84)	770 (16.2%)	-30.0% (0.70)
Service Component*				
Army [a]	8,790 (46.1%)	24.0% (1.24)	2,387 (50%)	35.0% (1.35)
Air Force [b]	3,709 (19.5%)	-21.0% (0.79)	1,017 (21%)	-14.0% (0.86)
Navy [a]	5,525 (28.9%)	22.0% (1.22)	1,144 (24%)	2.0% (1.02)
Marine Corps [b]	1,041 (5.5%)	-62.0% (0.38)	209 (4%)	-70.0% (0.30)
Military Pay Grade*				
E-1 to E-4 [b]	3,279 (17.2%)	-60.0% (0.40)	933 (19.6%)	-54.0% (0.46)
E-5 to E-9 [a]	12,727 (66.8%)	71.0% (1.71)	3,188 (67.0%)	72.0% (1.72)
O-1/WO1 to O-3/CW3 [b]	1,026 (5.4%)	-51.0% (0.49)	200 (4.2%)	-62.0% (0.38)
O-4/CW4 to O-6/CW5 [a]	2,031 (10.7%)	52.0% (1.52)	435 (9.1%)	31.0% (1.31)

Note: Military composition percentages provided by the DMED. * indicates significance at $p < .001$. [a] denotes more cases than expected. [b] denotes fewer cases than expected. E-1 to E-4 and E-5 to E-9: represents enlisted. O-1(WO1) to O-3 (CW3) and O-4 (CW4) to O-6 (CW5): represents officers. PTSD = posttraumatic stress disorder. Observed vs. Expected counts represent the percentage of representation of cases ([O/E*100]-100) in relation to the expected percentage of cases, by demographic.

Many health risks and comorbid complications exist with T2DM, including ketoacidosis, hypo/hyperglycemia, cardiovascular disease, kidney disease, foot ulcers, amputations, visual impairment, depression, and anxiety.[10,11] From 2012 to 2017, the direct and indirect cost of diabetes-related care in the US increased by 26% to a staggering $327 billion.[12] Indirect costs were responsible for $89.9 billion and had a negative impact through 1) absenteeism; 2) reduced work productivity; 3) reduced productivity for those not in the workforce; 4) inability to work because of disease-related disability; and 5) premature deaths related to diabetes. Within the military health system, a study estimated the cost of diabetes care to be $1,684 per year, with a total cost of over $124 million.[13]

While previous studies have compared diabetes in the military to the general population, there are few studies examining trends of newly diagnosed service members.[3] The available studies are outdated and do not compare rates of T2DM within the military population across different age groups, enlisted or officer, sex, and race amongst active duty military members. The purpose of this study was to examine incidence rates of T2DM in a military population over a ten-year period and whether demographic characteristics differ within the same population. We hypothesize there will be a continued increase in incidence rates of T2DM and differences within demographic variables over the ten-year period.

Methods

The Institutional Review Board at the 59th Medical Wing, Wilford Hall Medical Center, reviewed this study and deemed it exempt research because the data provided by Defense Medical Epidemiological Database (DMED) is de-identified and does not allow for linking back to individuals. This epidemiological study is a retrospective comparison trend analysis looking at rates of T2DM with and without complications based on initial diagnosis amongst the US military service components from 2006-2015, comparing rates amongst various age groups, military status (enlisted or officers), marital status, sex, and race. Data were derived from the Defense Medical Surveillance System stored within the DMED from 2006-2015. The DoD validates all the data within DMED and reports sex, age, race, military pay grade, marital status, and service component. The DMED tracks medical events and disease data pertinent to US military service members and categorizes data by hospitalization, ambulatory status, reportable events data, and demographics, as well as provides International Classification of Disorders (ICD) codes 9 for different medical diagnoses. Type 2 diabetes mellitus diagnoses within the first occurrence and ambulatory visits category (i.e., the first T2DM diagnosis documented within the electronic medical health record) were examined to ensure incidence rates were not overestimated. The data extracted from DMED only allow comparisons at the population level due to data being group-level counts.

Figure 1. Average incidence rates of type 2 diabetes without and with complications from 2006 - 2015.

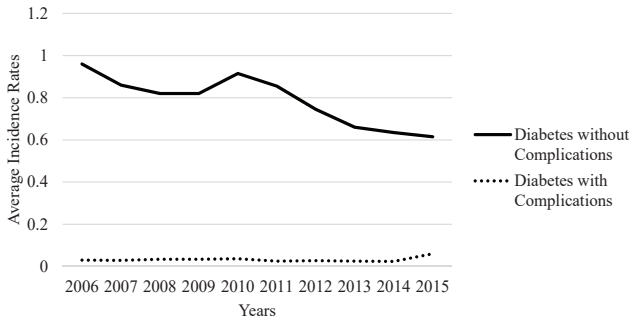
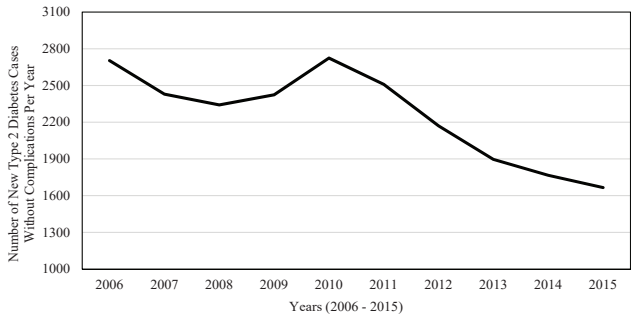


Figure 2. Counts of initial diagnoses of type 2 diabetes without complications counts by year, 2006 - 2015 (N=19,064).



Data were accessed on January 28, 2019, and were only screened for the following initial ICD-9 diagnoses: Diabetes Mellitus without mention of complication Type 2 (250.00 & 250.02), diabetes with ketoacidosis Type 2 (250.10), Diabetes with hyperosmolarity type 2 (250.20), Diabetes with other coma Type 2 (250.30), Diabetes with renal manifestations Type 2 (250.40), diabetes with ophthalmic manifestations Type 2 (250.50), Diabetes with neurologic manifestations Type 2 (250.60), Diabetes with peripheral circulatory disorders Type 2 (250.70), and Diabetes with other specified manifestations Type 2 (250.80). All Type 2 with complications were combined to assess for total presence. Due to the limitations in DMED, it is unclear where a diagnosis of Type 2 Diabetes was made (e.g., hospital admittance, routine annual physical or hospital appointment).

Statistical Analysis: T2DM incidence within each available demographic (e.g., sex, age, marital status, military pay grade, the branch of service, and race) were examined. Initially, the nonparametric one-sample chi-square goodness of fit test was used to determine over or under-representation of demographic subgroups of diabetes diagnoses relative to the hypothesized distribution within the entire military. The hypothesized distributions for each military composition variable used to derive expected values for each test were provided with the DMED data at the time of extraction. The diagnosed counts of diabetes within each composition variable was compared to military population distributions drawn from DMED to derive the observed-expected ratios. Follow-on chi-square analyses were conducted to assess for between-group differences amongst T2DM with and without complications. The mean population of service members each year in the DMED data was 1,375,484, with a range from 1,302,810 service members in the active force in 2015 to 1,418,896 service members in the active force in 2010.

Results

Between 2006 and 2015, 23,821 active duty service members received an initial diagnosis of T2DM (Table 1). The incidence rates in the U.S. military ranged from 0.22 (per 1,000) in 2015 to a high of 1.46 (per 1,000) in 2006 for T2DM without complications and 0.00 (per 1,000) in 2007 to a high of 0.29 (per 1,000) in 2015 for T2DM with complications (Figure 1).

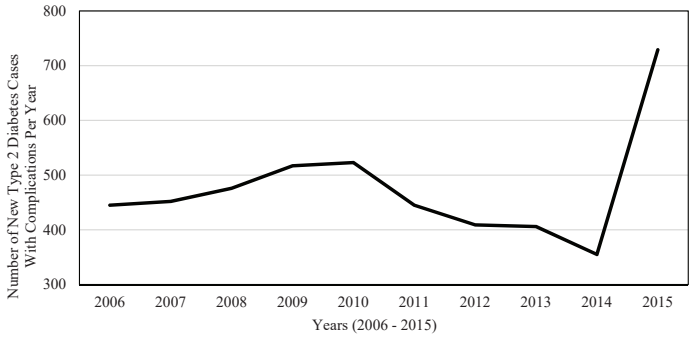
Type 2 Diabetes without Complications: Between 2006 and 2015, 19,064 active duty service members were diagnosed with T2DM without complications (Figure 2). In the present sample, T2DM without complications was found to significantly differ in terms of observed distributions and expected distributions for sex X2 (1, 19,065)=59.64, p<0.001, age, X2 (5, 19,065) =28,909.02, p<0.001; marital status, X2 (1, 19,065) =2,109.77, p<0.001, race, X2 (2, 19,065)=3,122.58, p<0.001, service branch, X2 (3, 19,065)=1,917.46, p<0.001, and pay grade, X2 (3, 19,065)=7,643.25, p<0.001 (Table 2). In the present sample, those most often diagnosed with

Table 2. Summary of demographics counts by age from 2001 to 2017 for type 2 diabetes without complications.

	Age (Years)					
	< 20	20 – 24	25 – 29	30 – 34	35 – 39	≥ 40
Gender						
Male	55	282	313	344	668	1501
Female	11	64	74	68	64	160
Marital Status						
Married	12	138	236	316	593	1380
Not Married	54	208	151	96	139	281
Race						
White	45	241	240	194	313	633
Black	13	83	107	160	303	704
Other	8	22	40	58	116	324
Service Branch						
Army	22	163	196	206	343	904
Air Force	15	80	80	81	158	345
Navy	9	56	85	105	211	372
Marine Corps	20	47	26	20	20	40
Military Pay Grade						
E-1 to E-4	66	304	175	81	43	52
E-5 to E-9	0	36	183	293	612	1249
O-1 to O-3 (W1 – W3)	0	6	29	30	44	54
O-4 to O-6 (W4 – W5)	0	0	0	8	32	306

T2DM without complications were married (76.3%), in the enlisted pay grade of E-5 to E-9 (66.8%), white (48.3%), males (87.0%), in the Army (46.1%), and were 40 years of age or older (46.2%). The average incidence rate over the study period was 0.79 (per 1,000).

Figure 3. Counts of initial diagnoses of type 2 diabetes with complications by year, 2006 - 2015 (N=4,757).



Type 2 Diabetes with Complications: Between 2006 and 2015, 4,757 active duty service members were diagnosed with T2DM with complications (Figure 3). In the present sample, T2DM with complications was collected using the collapsed variable to indicate any complications associated with T2DM. T2DM with complications was found to significantly differ in terms of observed distributions and expected distributions for sex, X2 (1, 4,757)=44.10, p<0.001, age, X2 (5, 4,757)=7,107.10, p<0.001; marital status, X2 (1, 4,757)=424.06, p<0.001, race, X2 (2, 4,757)=1,672.99, p<0.001, service branch, X2 (3, 4,757)=572.97, p<0.001, and pay grade, X2 (3, 4,756)=1,793.85, p<0.001 (Table 3). In the present sample, those most often diagnosed with T2DM with complications were married (74.6%), in the enlisted pay grade of E-5 to E-9 (67.0%), white (44.5%), males (88.4%), in the Army (50.0%), and were 40 years of age or older (46.1%). The average incidence rate over the study period was 0.03 (per 1,000).

Discussion

The incidence rates of T2DM has increased in the US, estimating a prevalence of 8-12% of the population in recent years and an incidence rate of approximately 7 per 1,000 persons.[12,17,18] Factors contributing to this include obesity and metabolic syndrome, which continue to be more prevalent in the US. The results of this study found rates of T2DM with and without complications that are lower than civilian studies and were consistent with previous military studies.[4,5] The low incidence rates may provide insight into a benefit of the military culture. Previous research has reported that low incidence of T2DM in the military may be a byproduct of the promotion and emphasis of weight control, exercise, and physical activities.[19]

It is unclear why there was a slight increase in the incidence rate of T2DM patients from 2009 to 2010 and a decreasing trend from 2010 to 2015. A potential confounder for the slight increase could be due to the growth of the general military population, which peaked in 2010. In contrast, the large-scale reduction in forces that started in 2012 may partially explain the decrease in incidence of T2DM from 2010 to 2015.[20]

T2DM was more commonly diagnosed in individuals 40 years and older, similar to patterns in the general US population, which currently estimates incidence rates in adults 45-64 years old to be 10.9 per 1,000 adults and those 65 years and older to be 9.4 per 1,000 adults.[21] Similarly, the observed incidence rates of T2DM were more common in higher non-commissioned ranks E5 to E9, as a promotion to higher ranks is typically commensurate with time, merit, and age. Finally, when comparing rates between enlisted members and commissioned officers irrespective of age, there were similar numbers for junior enlisted (E-1 – E-4) and junior officers (O-1 – O-3). The same trend was similar for senior enlisted (E-5 – E-9) and senior officers. The higher rate of T2DM in members in the rank of E1-E-4 as compared to officers in the rank of O-4/CW4 to O-6/CW5 may be confounded by differences of socioeconomic classes and the level of education between these two groups. There is also a disproportionate amount of enlisted to commissioned officers in the overall Armed Forces as the observed-to-expected ratios are comparable. As of July

Table 3. Summary of demographics counts by age from 2001 to 2017 for type 2 diabetes with complications.

	Age (years)					
	< 20	20 – 24	25 – 29	30 – 34	35 – 39	≥ 40
Gender						
Male	149	1,227	1,852	2,241	4,340	9,200
Female	64	405	459	439	481	866
Marital Status						
Married	28	727	1,547	2,056	3,928	8,525
Not Married	185	905	764	624	893	1,541
Race						
White	136	1,078	1,301	1,282	2,177	4,497
Black	51	349	631	877	1,790	3,416
Other	26	205	379	521	854	2,153
Service Branch						
Army	84	729	1,065	1,188	2,079	4,890
Air Force	27	332	443	537	990	2,037
Navy	62	364	601	813	1,558	2,875
Marine Corps	40	207	202	142	194	264
Military Pay Grade						
E-1 to E-4	213	1,368	944	478	336	270
E-5 to E-9	0	224	1,215	1,952	4,015	7,365
O-1 to O-3 (W1 – W3)	0	40	152	193	256	462
O-4 to O-6 (W4 – W5)	0	0	0	57	212	1,969

2019, there were 1,085,107 enlisted personnel as compared to only 234,216 officers across the four branches (Air Force, Army, Marines, and Navy).[22]

The differences between sex and ethnicity differences seen in the military population were similar to those trends seen in the general US population. Although men typically had a higher incidence of T2DM, there was a lower observed than expected incidence of T2DM in the military women. These trends could be due to more athletic women joining and remaining in the US military. The differences in races may be accounted for by the more predominant overall number of white service members than black service members as the observed-to-expected ratio of black service members was much greater than the observed-to-expected ratio of white service members. Finally, of note, the incidence of married military members with T2DM was larger than expected and more extensive compared to those unmarried. Potential factors to explain these results may be an older age population or having less free time to spend on self-care in the married group.

Spending on healthcare related to diabetes mellitus and its complications has increased substantially and poses a significant challenge to the US. The average health care expenditure attributed to patients with diabetes in 2017 was estimated to be $6,675 and $13,239 per patient aged under and over 65, respectively.[13] Even though a new diagnosis of T2DM does not disqualify an active duty member from retaining their job, these members are required to undergo additional medical visits to ensure their diabetes is well controlled and does not interfere with their primary job or deployability. This likely adds to the average healthcare expenditure for the overall treatment of these patients.

Between 2006 and 2015, a small number of the US military were diagnosed with T2DM. Contrary to our hypothesis, however, the incidence rates of T2DM appears to be gradually decreasing during this time, although there was an increase in those with a history of complications in 2015. Knowing that T2DM typically presents in more experienced and high ranking members, it will be a continued burden upon the US military that needs to be addressed. Further studies analyzing more recent trends and the incidence rates of both T2DM and Type 1 diabetes mellitus would be required to determine the full extent of diabetes on military readiness.

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Authors

Tyler L. Collette is Post Doctoral Fellow, Office of Research at Kennesaw State University amd University of Texas at San Antonio.

Jason L. Judkins is Research Occupational Therapist, Military Performance at University of Texas at San Antonio, Uniformed Services University, and San Antonio Uniformed Services Health Education Consortium.

Morgan Gettle is Medical Director, Flight Surgeon, 86 OMRS, Ramstein AB, Germany, and with San Antonio Uniformed Services Health Education Consortium.

Brian A. Moore is Assistant Professor, Psychology, Kennesaw State University, and with University of Texas Health Science Center at San Antonio.

Michelle Lee is Endocrinology Fellow, San Antonio Uniformed Services Health Education Consortium, and with Diabetes Center of Excellence, Wilford Hall Ambulatory Surgical Center.

Darrick Beckman is Medical Director, Diabetes Center of Excellence, Diabetes Center of Excellence, Wilford Hall Ambulatory Surgical Center.

Mari-Amanda Dyal is Assistant Professor, Public Health, Kennesaw State University.

Ashton Rouskais with University of Texas at San Antonio and San Antonio Uniformed Services Health Education Consortium.

Joshua Tate is Endocrinologist, Keesler Medical Center. Keesler Air Force Base, and with Diabetes Center of Excellence, Wilford Hall Ambulatory Surgical Center.

Jana L. Wardian is Assistant Professor, College of Med, and with Diabetes Center of Excellence, Wilford Hall Ambulatory Surgical Center.

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Transcorneal Freezing in Aged Rabbits as a Platform for Evaluating Corneal Endothelial Cell Therapeutics

Lauren E. Cornell, MSc, PhD
Eric J. Snider, PhD
Jennifer S. McDaniel, PhD
Randolph Glickman
COL (ret) Anthony Johnson, MD
David Zamora, PhD

Abstract

Purpose: Transcorneal freezing is a common technique used in rabbits to induce damage to the corneal endothelium. Previous studies have been performed with a range of freezing temperatures, times, and rabbit ages. Here, we aimed to characterize the aged rabbit endothelium after transcorneal freezing to establish an innate corneal endothelial cell regrowth rate and propose it as a mechanism for evaluation of therapeutic efficacy in rabbit models.

Methods: Central corneas of anesthetized New Zealand White rabbits (n=3) aged 18-24 months were exposed to nitrous oxide cooled probes for 30 seconds. Animals were assessed by in vivo confocal microscopy, applanation tonometry, specular microscopy, optical coherence tomography, and histology. The contralateral eye acted as a control. Images were taken immediately before and after injury and on days 2, 4, 7, 11, and 14.

Results: Following transcorneal freezing, there was a significant decrease in corneal endothelium density and a temporary increase in corneal thickness. Endothelial density decreased by 95% immediately after injury compared to controls and showed linear recovery over 14 days, reaching a 38% reduction by day 14. There was a significant increase in pleomorphism across all time points post-injury. Conversely, corneal thickness increased two days post injury but recovered at all later time points. Intraocular pressure was not affected throughout.

Conclusions: This corneal endothelium injury platform is ideal for injury and therapeutic research as it can be rapidly performed, and has minimal impact on corneal thickness and intraocular pressure. Due to innate rabbit endothelial regrowth, it is vital to establish corneal endothelial recovery rate before evaluating therapeutics for efficacy in this model system.

Keywords: transcorneal freezing, corneal endothelium, aged rabbits, animal disease model, regenerative medicine

Introduction

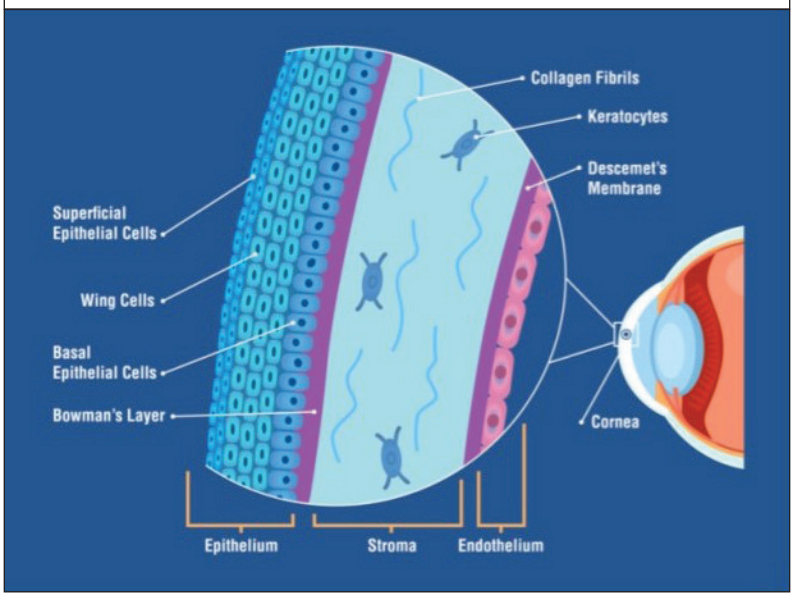
Civilians and soldiers alike experience loss of corneal endothelial cells (CEC), whether it be progressively with age, disease, or following acute ocular injury.[1,2] Injury to the cornea and anterior segment is particularly serious if the endothelial cell layer (Figure 1) is damaged, due to the eye's limited capacity to regenerate corneal endothelial cells (CECs).[3,4] A significant reduction in the density of CECs results in limited corneal hydration control, which may lead to corneal edema.[5]

While there are numerous causes of CEC loss that may affect the civilian population, such as dry eye[6] and dystrophies,[7] the modern warfighter is particularly vulnerable to corneal damage, due to a variety of ocular traumas on the battlefield. These may include explosives, chemical burns, and blunt trauma, which can cause visual damage or dysfunction with short- to long-term side effects.[8,9]

A notable cause for military relevant corneal injuries is the increased usage of improvised explosive devices

(IEDs). Blast waves generated from IEDs may project large and small shards of metal and other materials, greatly increasing the risk of ocular foreign body injuries to soldiers.[11,12] These penetrating injuries are a significant cause of corneal scarring and endothelial cell loss.[13] Additionally, it has been noted that blast injuries result in significant CEC loss on the side closest to the blast.[14]

Figure 1. Basic composition of the human cornea with cell layers defined.[10]



No matter the cause, with extensive CEC loss, the cornea cannot maintain optical transparency, and a corneal transplant, the current standard of care, will be needed. Due to the numerous sources of CEC dysfunction and limited treatment options, corneal transplantation is considered to be the most common type of tissue transplanted worldwide.[15]

The average military patient requiring hospitalization for ocular injuries is between the ages of 20-24.[16] Due to the nature of corneal transplants and the complications seen in military injuries, such as neovascularization and inflammation,[17] multiple corneal transplants may be needed throughout the individual's lifetime limiting their quality of life and return-to-duty rate. As a result, therapies to boost the native CEC density without requiring a corneal transplant could improve civilian and military healthcare. However, in order to develop these alternative medical approaches, an appropriate animal model and injury mechanism must be established and characterized.

Rabbits have been traditionally used as an optimal animal model for corneal and corneal endothelial studies due to the similarity in size and shape of their corneas to those of humans. However, unlike in humans, rabbits retain the ability to regenerate CECs.[18,19] Despite this, it remains a popular model for evaluation of corneal endothelial therapeutics.[20-23] Herein, we utilized this classic animal model, but worked exclusively with aged rabbits (18-24 months), which have been shown to have reduced CEC regeneration upon injury,[24] in order to mimic more closely the human conditions.

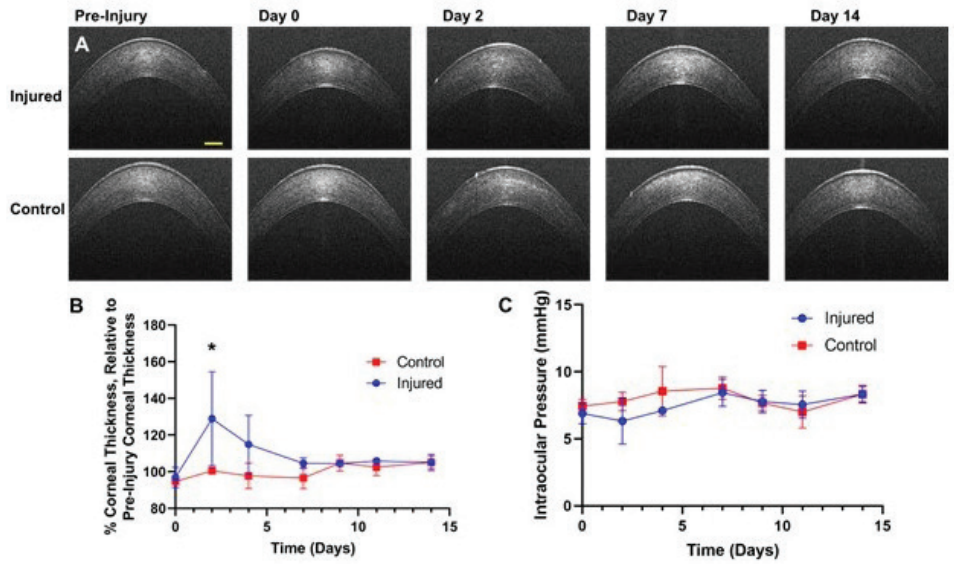
Our injury mechanism of choice, transcorneal freezing, has been utilized to damage or remove the corneal endothelium (CE) in both rabbits and humans.[25-29] While ocular cryotherapies have been exclusively developed for use in humans, in rabbit studies there have been a variety of mechanisms used, from cryostat units to pre-chilled probes of varying materials. Several techniques have been published, but the findings are limited as reported values vary in both temperature and duration of the corneal freeze. An alternative option to CEC removal is to mechanically remove the cells from the posterior surface of the cornea.[30,31] However, the use of transcorneal freezing is preferred in comparison to surgical CEC removal due to improved injury reproducibility and less technically challenging methodology resulting in a more universally accessible approach requiring less training, surgeries, and anesthesia duration on rabbits.

Materials & Methods

Animals: Research was conducted in compliance with the Animal Welfare Act, the implementing Animal Welfare Regulations, and the principles of the Guide for the Care and Use of Laboratory Animals, National Research Council. The facility's Institutional Animal Care and Use Committee approved all research conducted in this study. The facility where this research was conducted is fully accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC). For this study, female New Zealand White rabbits aged 18-24 months were used due to their breeder status allowing for a more advanced age. Upon transfer to the US Army Institute of Surgical Research (USAISR) animal facilities, rabbits were given a 10-day acclimation period before experimentation. Animals were anesthetized for all of the following procedures.

Procedure: Two drops of 0.5% Tetracaine hydrochloride were applied to the cornea and allowed to absorb to ensure there was no excess liquid on the ocular surface. A

Figure 2. (A) Representative optical coherence tomography (OCT) images for injured (top row) and control (bottom row) eyes, pre-injury and 0, 2, 7, and 14 days post-injury. Scale bar denotes 0.5 mm. (B) Change in central corneal thickness as determined by OCT between control (red) and injured eyes (blue). Measurements are shown as percent changes relative to pre-injury corneal thickness measurements. (C) Intraocular pressure measurements for control (red) and injured (blue) eyes. Error bars denote standard deviation throughout (n=3). Asterisks denote significant differences ($p<0.05$) between control and injury values as determined by 2-way Analysis of Variance (ANOVA), post hoc Sidak analysis.



cryoprobe unit in conjunction with a 3.0 mm glaucoma probe utilizing nitrous oxide was used to create a cryo-injury on the surface of the rabbit cornea. The probe was allowed to cool until frost appeared on the probe (approximately 60 seconds), before placing on the central cornea for 30 seconds. It is important to ensure the probe is cooled before being placed on the rabbit cornea. Following the injury, Basic Salt Solution (BSS) was applied to the cornea to thaw the cryoadhesion and the probe was gently removed. For all rabbits, the left eye acted as the experimental eye (injured) while the right eye acted as the control. For the control eye, the same experimental procedures were followed with the probe remaining at room temperature. Both rabbit eyes were evaluated on day 0 before and after injury, with follow up imaging on days 2, 4, 7, 9, 11, and 14.

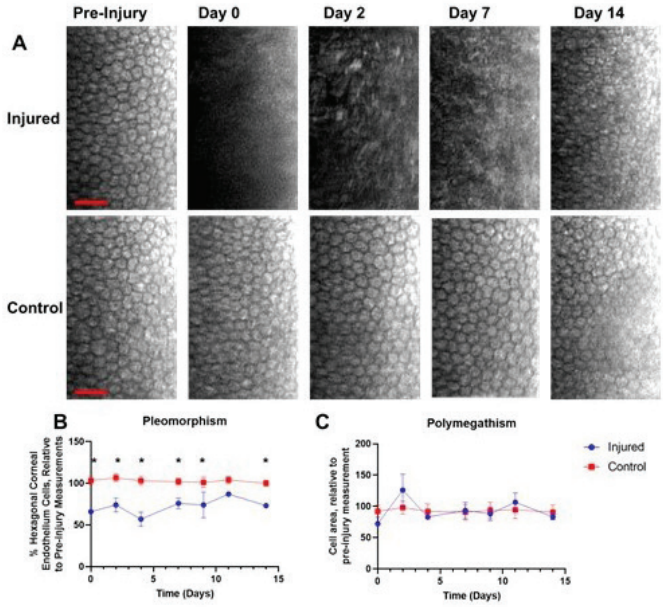
Ocular Assessments: Prior to and post injury, in vivo ocular assessments were performed for both eyes on all animals by intraocular pressure (IOP) readings, optical coherence tomography, specular microscopy, and in vivo confocal microscopy. To aid in animal comfort, BSS solution was applied to the rabbit corneas between imaging techniques.

- Intraocular Pressure: IOP readings for both eyes were collected within 10 minutes post anesthesia, in triplicate. These values were averaged together to produce a final IOP value.
- Optical Coherence Tomography: Image scans (8 x 8 mm area) were taken of the central cornea. Representative images of the central cornea were selected. Image sets were analyzed by measuring the corneal thickness at 35 points near the corneal apex and averaging, utilizing the caliber bars.
- Specular Microscopy: Rabbit eyes were moistened with BSS between specular images as needed. Paracentral images were captured at eight points, one central and seven surrounding images, at a 5º visual angle. For each point, 16 images were captured and automatically sorted for quality. The autoanalysis feature of the specular microscope provided corneal endothelial density as well as two histograms of variation in shape (pleomorphism) and size (polymegathism). These data were used to determine changes in corneal endothelial density, pleomorphism, and polymegathism. Corneal endothelium counts were performed from specular micrographs by using a rolling ball background subtraction algorithm32 to reduce local background discrepancies. Images were then binarized and cell counts were calculated using identical settings for all images. Cell counts were averaged across the central and paracentral cornea for each eye per time point and set relative to micrograph area (0.25 x 0.55mm) to determine CE density.

For pleomorphism analysis, the precent change from hexagonal cells was calculated by comparing pre-injury hexagonal cells counts to post-injury counts.

- In vivo confocal microscopy: Opthalmic solution was applied to the cornea before imaging. Images were taken scanning down from the corneal epithelium, to the stroma, and finally to the corneal endothelium. At least two image stacks were taken for each layer. Resulting image stacks were first aligned using a Scale-Invariant Feature Transform algorithm 33 followed by reducing stacks to a single image through maximum intensity projection mapping.

Figure 3. (A) Representative specular micrographs of the corneal endothelium, pre-injury and Days 0, 2, 7, and 14 post-injury for injured (top row) and control (bottom row) eyes. Scale bar denotes 50 µm. (B) Change in pleomorphism, as indicated by % of corneal endothelial cells (CECs) with hexagonal shape for injured (blue line) and control eyes (red line). Data are shown as a percentage relative to measurements taken pre-injury. (C) CEC area or polymegathism for injured (blue line) and control (red line) eyes. Data is shown as a percentage relative to measurements taken pre-injury. Scale bars denote standard deviation (n=3). Asterisks denote significant differences ($p<0.05$) between control and injury values as determined by 2-way Analysis of Variance (ANOVA), post hoc Sidak analysis.



Histology of Whole Globes: On day 14 after image analysis, rabbit eyes were enucleated for histopathological processing. Whole globes were fixed for 24 hours and then transferred to 10% neutral buffered formalin. Eyes were hemisected to isolate the anterior segment. Non-corneal tissues were removed, followed by bisecting the central cornea. Corneal tissue was embedded in paraffin for sagittal tissue analysis, serial sectioned at a 7 µm thickness, and stained with hematoxylin and eosin (H&E). Slides were imaged by slide scanner with a 20x objective to create tile maps of the entire corneal tissue for all slides.

Statistical Analysis: Technical replicates acquired from the various data acquisition methods were averaged prior to statistical analysis of triplicate biological replicates. Throughout, results are shown relative to pre-injury measurements that were collected for injured and control tissue. First, we determined if parametric analysis was valid for this study by evaluating normality by the Shapiro-Wilk test (null hypothesis = normally distributed, $p<0.05$). For this study, all comparisons were found to be suitable for parametric analysis. Two-way Analysis of Variance (ANOVA) was used to assess statistical differences across the 14-day time course (Factor 1) and as a result of the transcorneal freezing (Factor 2). Sidak post-hoc test ($p<0.05$) was used to determine signifant differences between control and injured eyes at each time point.

Results

Effect of Transcorneal Freezing on Corneal Thickness & IOP: Following transcorneal freezing, we first evaluated changes to corneal thickness through optical coherence tomography and compared results to pre-injury thickness values. Qualitatively, no changes in light scattering in Optical Coherence Tomography (OCT) images were detected indicating corneal opacity was minimally altered (Figure 2A). Thickness of the central cornea was found to be significantly increased by approximately 40% two days post-injury, compared to pre-injury controls (Figure 2B). Interestingly, this effect was reversible and recovered by day 7 to pre-injury thickness measurements. Conversely, IOP was found to be similar between injured and control measurements at all time points across the 14-day study. Overall, these results suggest the side effects of the transcorneal freezing to the cornea beyond CE injury are minimal, reducing potential confounding factors in this injury model.

Effect of Transcorneal Freezing on Corneal Endothelium: Specular microscopy was used to evaluate endothelial density, size, and shape (Figure 3A). For each image of the central cornea taken, the microscope provided values on pleomorphism, polymegathism, and endothelial density. These values were captured and graphed over the 14-day period. There was a significant change

Figure 4. Percent corneal endothelial density relative to pre-injury corneal endothelial (CE) density measurement for control (red line) and injured (blue line) eyes. Scale bars denote standard deviation (n=3). Linear fit equation for injured eye CE density vs. time (days) is shown. Asterisks denote significant differences ($p<0.05$) between control and injury values as determined by 2-way Analysis of Variance (ANOVA), post hoc Sidak analysis R=.9764.

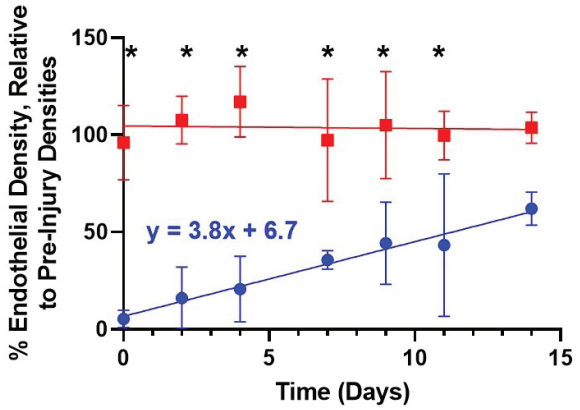
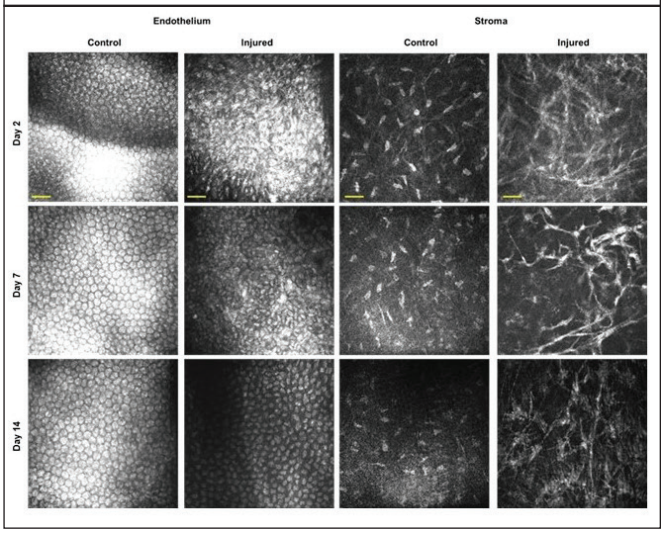


Figure 5. Representative confocal micrographs of the corneal endothelium and stromal tissue on days 2, 7, and 14 for injured and control eyes. Scale bars denote 50 µm.

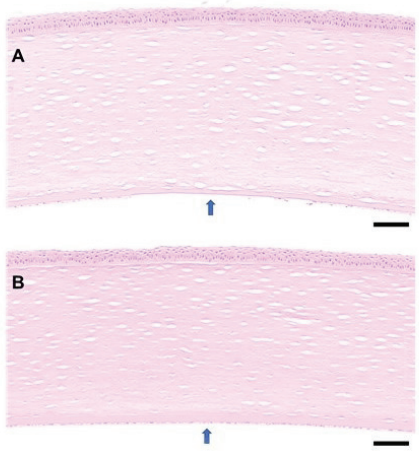


in pleomorphism (cellular shape) across all time points except on day 11 post-injury (Figure 3B) when comparing the percent of hexagonal cells for each time point relative to pre-injury. CECs transitioned from hexaganol to either heptagonal or pentagonal with no trend toward either direction. However, polymegathism, or variation in the cellular size of the corneal endothelial cells, did not significantly change (Figure 3C). We next quantified cell number in each specular 0.25mm x 0.55mm micrograph to measure CEC density. CEC density decreased by 95% immediately after injury compared to pre-injury measurement (Figure 4). While aged rabbits were used to reduce the rate of endothelial regrowth, there was still a CEC recovery over 14 days, resulting in a 38% reduction in CE density by day 14. Interestingly, CEC recovery strongly fit a linear relationship as a function of days post-injury (R2=0.976).

In Vivo Image Analysis of the Endothelium & Stroma: Confocal microscopy was performed to evaluate corneal endothelium integrity and stromal cell morphology. In agreement with specular microscopy results, the corneal endothelium displayed changes in density and cellular morphology apparent across all time points (Figure 5). In addition, recovery of the CE is apparent across the 14-day time course, with notable differences in CE density throughout when compared to control eyes. Further, stromal tissue from injured corneas appeared to have increased striations as compared to controls.

Histological Analysis of Corneal Tissue: Hematoxylin and eosin (H&E) staining was performed on sagittal sections of the corneal tissue to assess morphological changes. Descemet's membrane remained intact in both injured and control eyes (Figure 6). However, CECs on the membrane were either reduced or absent near the injury site, which was not observed in contralateral control tissues (Figure 6).

Figure 6. (A) Hematoxylin and eosin (H&E) stain of a representative injured cornea enucleated on day 14. Descemet's membrane remains intact with a disturbance in the corneal endotheial cell population noted in the central corneal (arrow). The injury area is within the transcorneal freezing zone. (B) H&E stain of a representative control cornea enucleated on day 14. Descemet's membrane and the corneal endothelium remain intact (arrow) despite having a room temperature probe placed on the corneal surface. Scale bars denote 100 µm.



Discussion

To date, the loss of corneal endothelial cells, through injury or dysfunction, can only be treated with a corneal tissue transplant.[7,15] The current standard of care, corneal transplantation, has numerous drawbacks including graft rejection, cellular loss, and neovascularization after transplantation.[34] Further, there is a tissue shortage worldwide.[15] To address this shortage and to improve the outcomes associated with corneal

damage, alternative therapeutic interventions must be developed. In experimental investigation, rabbits are commonly used in corneal endothelial studies due to their anatomical similarities to humans in corneal size and thickness. However, unlike humans, rabbits have in vivo endothelial regeneration capabilities, the rate of which varies with age.[18,19] In order to appropriately assess these novel interventions, a standardized model of corneal endothelial damage and rate of innate corneal endothelial regrowth must be established in a rabbit model.

Mechanical scraping and surgical removal of Descemet's membrane are common approaches to reduce CEC density.[31,35,36] However, due to the surgical nature of these techniques, there may be variability injury to injury. In order to control injury severity and reduce damage to corneal tissues outside of the endothelium, transcorneal freezing was the injury mechanism of choice for these studies. Transcorneal freezing to the corneal surface has been utilized as a mechanism for creating corneal endothelial injuries with minimal damage to the surrounding corneal structures, such as bowman's layer and epithelial cells, creating an endothelial focused injury.[25,37] While the use of transcorneal freezing in New Zealand rabbits is widespread, a standardized transcorneal freezing corneal endothelial injury model has not been established for therapeutic research studies. Multiple probe sizes, temperatures, injury durations, and cooling techniques have been used with ranging results.[24,25,27,38,39] Further, rabbit age is often not disclosed despite being documented to have an effect on corneal endothelial regeneration capabilities and rate of recovery.[24] The ability to regenerate the endothelium and the rate at which it recovers may impact the effecicacy findings of potential therapeutics.

For example, a study by Goldberg et al using adult New Zealand rabbits (no specific age cited) showed that after CE damage and introduction of human cells, it was difficult to observe the difference between rabbit cells and the intended therapeutic at 3 months, due to innate rabbit regrowth of CEC. However, migration of these cells was noted by post operative day 7.[40] Therefore, knowledge of an established innate endothelial recovery rate following injury, is essential for proper study design and may aid in development and efficacy analysis of drugs or therapeutic developments. Herein, we provide data supporting the efficacy of transcorneal freezing for use in aged New Zealand rabbits, establish a linear regrowth rate of CECs, an ideal time frame for therapeutic evaluation, and propose it as a standardized method of corneal endothelial damage.

We found the use of transcorneal freezing was an effective method of damaging the corneal endothelial. This was determined damage based on multiple factors, including a significant reduction in CECs, which was observed using specular imaging, confocal microscopy, confocal microscopy, and histology. Further, of the cells remaining after injury, there was a significant reduction in the number of hexagonal corneal endothelial cells, further establishing CE injury. CECs transitioned from hexaganol to either heptagonal or pentagonal with no trend toward either direction other than a significant change in population from primarily hexagonal (Figure 3B), indicating stress or injury to the CEC population.[7] While a significant change in corneal thickness did occur (Figure 2), it resolved by the day 4 timepoint. However, this timeline could be extended if a longer freeze time was used.

While there are a range of reported freezing times, we selected a 30-second timepoint for corneal endothelial damage as it was used both in studies utizilizing cryostat units and probes for transcorneal freezing.[24,25,29,38,41,42] Thirty seconds of transcorneal freezing produced an injury that was effective at removal of CECs with minimal impact on corneal thickness. Furthermore, we chose a 14-day end point as this was the reported average timeframe for corneal endothelial recovery in a rabbit model.[28] Upon accumulation of CE cellular counts across the study, a strong linear relationship (R2=0.976) between corneal endothelial density and time (from injury through 14 days) was found. Even though the injury region started with less than 10% of the original CECs, the endothelium recovered at a rate of approximately 4% per day. This rate is much quicker than human CEC growth rates, which is why this rate must be accounted but is slower than previous studies tracking this growth rate in adult rabbits.[28,43] These results highlight the need for aged rabbits when evaluating corneal endothelial damage and therapeutics. Doughty et al proposed that white New Zealand rabbits at a minimum age of nine months are preferred for CE studies;[18] however, these results suggest a significant CEC recovery over the 14 days post-injury was still obtained with the use of rabbits aged 24 months. We observed a significant recovery of the endothelium over a 2-week period despite a significant reduction in corneal endothelial density.

Based upon the established linear progression in aged rabbits and corneal response to transcorneal injury, we suggest CE therapeutic interventions be implemented 4 days post-injury. At this point, the CE population was still significantly lowered from its pre-injury baseline, but the impacts on corneal thickness had mostly reverted to pre-injury levels. Interventions prior to 4 days post-injury could be impacted by the corneal thickness as a

confounding factor. Conversely, therapeutics administered after day 11 (such as delayed treatment evaluation scenarios) should be avoided as the CEC population was found to be recovered by the innate CE regenerative rate. A significant increase in the slope of the linear relationship between CEC density and time post-injury above the approximate 4% recovery rate we calculated would be needed for a therapeutic to have a positive impact on the CE. Overall, the linear relationship and proposed therapeutic intervention timeline are essential for use in other studies to properly account for innate endothelial recovery within the aged, white New Zealand rabbit model, resulting in better evaluation of CE therapeutics.

Alterations in the transcorneal freezing injury model could be introduced to better acertain aspect CE trauma. For instance, a larger CE injury area may be required. The literature has described the use of a variety of probe sizes (2.4mm–8.0mm diameter), with some reporting a doubling in the size of the injured area as compared to the probe size.[26] We found the 3.0mm probe to be effective for a centralized corneal injury with minimal damage to other corneal structures, but other sizes could be utilized for paracentral injuries or more severe trauma situations. Tracking injury progression would be similar for larger injury defects as was described for this study, but a large injury could simplify monitoring of the CE defect as it became increasingly difficult to locate in this study as the CEC density recovered. Another aspect of the injury model would be reduction of the CEC recovery rate due to cellular regeneration. However, different injury sizes are possible if a larger or smaller injury size is desired. Ideally, to mimic the human scenario, regeneration could be further suppressed and more complex model setups could potentially accommodate a range of human CE dysfunctions and injuries. Nonetheless, by having a strong linear correlation between CEC recovery and time, this is less of a concern in therapeutic evaluation. Efficacy could still be tracked by evaluating how the slope of the recovery is altered by the intervention with the established "injury window."

Next steps for this work would include evaluating the linear recovery rate of aged rabbits with larger transcorneal freezing areas and varying freeze times. Further, commercially available CE therapeutics will be evaluated to assess the relationship of established clinical CE recovery in humans and the CE recovery in this model to further standardize the process of evaluating CE therapeutic effectiveness and CEC recovery. This model could then be used to evaluate novel therapeutic interventions and correlate the results to predicted efficacy in clinical applications.

Overall, this characterized transcorneal freezing corneal endothelial injury platform is ideal for injury and therapeutic research for both practical and biological reasons. Practically, this technique is repeatable, can be accomplished in a matter of seconds, is non-invasive, requires minimal training, is commercially available, and is cost effective, making it simple to implement in other CE studies as an accessible option for many laboratories. Biologically, this technique creates a significant loss of corneal endothelial cells that can be tracked in multi-day studies while corneal thickness is minimally impacted. While rabbits continue to be the model of choice for corneal endothelial studies, the standardized transcorneal freezing injury mechanism and "injury window" we defined in this study are imperative to properly understand the effect of corneal endothelial therapeutics.

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Authors

Lauren E. Cornell is with Sensory Trauma Research Division, United States Army Institute of Surgical Research, Fort Sam Houston, TX.

Eric J. Snider is with Sensory Trauma Research Division, United States Army Institute of Surgical Research, Fort Sam Houston, TX.

Jennifer S. McDaniel is with Sensory Trauma Research Division, United States Army Institute of Surgical Research, Fort Sam Houston, TX.

Randolph Glickman is with Ophthalmology, University of Texas Health Science Center at San Antonio, San Antonio, TX.

COL (ret) Anthony Johnson is with Ophthalmology Department, San Antonio Military Medical Center, Fort Sam Houston, TX.

David Zamora is with Sensory Trauma Research Division, United States Army Institute of Surgical Research, Fort Sam Houston, TX.

Utilization of Neurophysiological Classification Systems in Determining Interventions for Patients with Carpal Tunnel Syndrome

Greg Ernst, PT, PhD, ECS
Scott W. Shaffer, PT, PhD, ECS
John S. Halle, PT, PhD, ECS
David G. Greathouse, PT, PhD, ECS, FAPTA

Abstract

Background: Median mononeuropathy at or distal to the wrist, or carpal tunnel syndrome (CTS), is the most common peripheral nerve compression disorder in the upper extremity. Neurophysiological classification systems for patients with CTS have been developed and implemented to provide health care providers an enhanced system of electrophysiological evaluation with a grading scale, so that they may evaluate their patients with CTS within a system that confers relative severity. Electrophysiological data collected within these classification systems includes either nerve conduction studies (NCS), or both NCS and electromyography (EMG) test results. The purpose of this study was to assess the utilization of neurophysiological classification systems in determining interventions for patients with carpal tunnel syndrome (CTS).

Methods: To assess the utilization of neurophysiological classification systems in determining interventions for patients with CTS, an on-line survey of referring providers to NCS/EMG (electrophysiological testing) clinics was developed. These clinical sites were asked to submit three referring providers of their NCS/EMG services. The survey was emailed to the referring providers with a letter of introduction that included an overview and purpose of the study and specifically stated their responses were completely anonymous and analyzed data would be in an aggregate form.

Results: Of the 35 referring providers of NCS/EMG services for their patients with CTS contacted to participate in this study, 14 providers completed the on-line survey (40%). This included 12 physicians (MD), one osteopathic physician (DO), and one nurse practitioner (NP). Twelve of the referring providers (85.7%) were familiar with clinical electrophysiological classification systems for patients with CTS. Nine referring providers use a neurophysiological classification system (Greathouse Ernst Hall Shaffer (GEHS) and Bland—six; GEHS only—two; alternate system—one). Five respondents did not use a neurophysiological classification system, two of which were not familiar with these classification systems. The nine providers who use a neurophysiological classification system for their patients with CTS found these systems useful in assessing patient prognosis, treatment planning, and communicating back to referral services. The most preferable treatments for the very mild and mild (sensory only; sensory and motor) classifications were splinting followed by oral medication and injection. Splinting and surgery (open and endoscopic) were the interventions of choice for the moderate/severe and severe electrophysiological classifications.

Conclusion: Referring providers of NCS/EMG services completed an on-line survey to assess the utilization of neurophysiological classification systems in determining interventions for patients with CTS. The most preferable treatments for the very mild and mild (sensory only; sensory and motor) classifications were splinting followed by oral medication and injection. Splinting and surgery (open and endoscopic) were the interventions of choice for the moderate/severe and severe electrophysiological classifications. A method for using a neurophysiological classification system for patients with CTS in a clinical report is provided. Additional research to assess the prognostic validity and utilization of carpal tunnel classification systems as longitudinal outcome measures is needed.

Keywords: median nerve, carpal tunnel syndrome, nerve conduction studies, electromyography, electrodiagnostics

Introduction

Median mononeuropathy at or distal to the wrist, or carpal tunnel syndrome (CTS), is the most common peripheral nerve compression disorder in the upper extremity.[1-4] CTS is one of a number of muscle, tendon, and nerve-related disorders that affect people performing intensive work with their hands.[5-7] CTS is defined by the American Academy of Orthopaedic Surgeons as a symptomatic compression neuropathy of the median nerve at the level of the wrist, characterized physiologically by evidence of increased pressure within the carpal tunnel and decreased function of the nerve at that level.[8]

A thorough history and physical examination are considered essential screening tools for detecting signs and symptoms of peripheral neuropathy.[9-12] Nerve conduction measurement is often performed on the median nerve to determine whether certain entrapment neuropathies are present. Nerve conduction studies (NCS) are considered the gold standard, and they have criterion-related validation when assessing the electrophysiological status of the peripheral nerve.[3,9-16] The electrophysiological examination including both NCS and electromyography (EMG) studies permit evaluation of a specific peripheral nerve, the location in the nerve pathway of potential pathology, involvement of sensory and/or motor axons, and the presence of myelinopathy and/or axonopathy neuropathic process.[10-12]

Different ways of expressing the severity of CTS using electrophysiological parameters are found in the existing literature and in clinical records.[17-20] In 2000, Bland documented the distribution of patients with CTS on a scale based upon NCS findings.[17] Bland created this CTS classification system largely independent of the exact normal values used in any given electrodiagnostic laboratory (e.g. a 'Table of Normal Values'), and this classification scale demonstrates a highly significant linear relationship between the neurophysiological grading and a numerical score derived from the clinical history.[17-18] In 2012, a new neurophysiological classification system for patients with CTS was introduced.[19] The Greathouse Ernst Hall Shaffer (GEHS) neurophysiological classification system for patients with CTS includes findings for both the NCS and EMG components of the electrophysiological examination. The GEHS classification system provides electrophysiological evidence of myelinopathy based on NCS values and a Table of Normal Values, and/or axonopathy for patients with CTS by incorporating the EMG component.[19]

The purpose of developing and implementing neurophysiological classification systems for patients with CTS is to provide health care providers an enhanced system of electrophysiological evaluation and grading scale so they may evaluate and treat their patients with CTS based on a systematic review of the data and placing the findings along a continuum that reflects severity. The Bland system utilizes NCS data, a physical exam, and patient history.[17] The GEHS classification system adds to this clinical picture the EMG data, in an attempt to provide an assessment based on the complete scope of the electrophysiological data collected.[19] How health care providers utilize the neurophysiological classification systems[17-20] in evaluating and treating their patients with CTS has not been determined. The purpose of this study was to assess the utilization of neurophysiological classification systems in determining interventions for patients with CTS.

Methods

Reviewed and approved by the Institutional Review Board, University of Texas Health Sciences Center San Antonio, the study aimed to assess the utilization of neurophysiological classification systems in determining management for patients with carpal tunnel syndrome (CTS). An on-line survey of referring providers to NCS/EMG (electrophysiological testing) clinics was developed, and the following research questions were used in the development of that survey:

1. Are the referring providers familiar with the Bland neurophysiological classification system for patients with CTS?

2. Are the referring providers familiar with the GEHS neurophysiological classification system for patients with CTS?

3. Do the referring providers use these neurophysiological classification systems for patients with CTS to determine interventions?

4. What are the interventions used by these referring providers for patients with CTS for each of the grades of neurophysiological classification system (early mild, mild, moderate, moderate/severe and severe)?

Board certified by the American Board of Physical Therapy Specialties, Clinical Electrophysiologists who perform NCS/EMG studies and use a neurophysiological classification system provided names and contact information of their referring providers. Twenty-two electrophysiological testing clinical sites initially volunteered to participate in the study. These EMG/NCS clinical sites were asked to submit three referring providers of their EMG/NCS services. Of the 22 clinical sites, 14 submitted at least one provider of their EMG/NCS services.

The providers who referred patients with possible CTS for electrophysiologic testing included physicians, nurse practitioners, physician assistants, and chiropractors.

The referring providers' names and email addresses were confidential, and only one investigator had access to this information. Fourteen EMG/NCS clinical sites provided the names/email addresses of 35 referring providers of their electrophysiological evaluation services. The survey was emailed to the 35 referring providers with a letter of introduction that included an overview and purpose of the study and specifically stated responses were completely anonymous. Investigators used a commercially available platform for the electronic delivery of the survey instrument.

Case Study

A male patient in his 40's presented with a referral for possible left CTS (median neuropathy at or distal to the wrist), based on diminished sensation in his thumb, index, middle, and ring finger for the past five years. No clear pain or weakness was reported in either upper extremity, and the patient denied any neck discomfort or limitations. The individual was not taking any over-the-counter or prescription medications, and apart from the presenting symptoms, he described himself as having good general health. The patient did state he had a relative (grandparent) with Type II diabetes, but no other known familial history of conditions that might impact the peripheral nervous system.

The scanning physical examination (upper quarter screen)[34] performed was unremarkable apart from decreased sensation over the palmar aspect of the left thumb, index finger, middle finger, and radial aspect of the ring finger, and the adjacent palm. Basic categories assessed as part of this scanning physical exam included range of motion, special tests like foraminal encroachment tests, manual muscle testing of the upper quarter bilaterally, sensation of the upper extremities bilaterally, muscle stretch reflexes, pathological reflexes, and other (such as observation for surgical scars, atrophy, etc). Apart from the sensory findings, the other components of the scanning physical examination were unremarkable.

The electrophysiological examination (NCS and EMG) demonstrated the following:

1. Absent left distal sensory latency (DSL) from palm-wrist (at a distance of 8 cm).

2. Absent left DSL from 2digit-wrist (at a distance of 14 cm).

3. Prolonged left distal motor latency (DML) from wrist to abductor pollicis brevis (APB) (8 cm distance), or 7.7 ms (normal<4.2 ms), with normal compound motor action potential (CMAP) amplitude of 5.1 mV (normal> 5.0 mV).

4. Normal left median nerve conduction velocity from the wrist to the cubital fossa of 53.8 m/sec (normal > 50 m/sec), with normal CMAP amplitude of 5.0 mV (normal > 5.0 mV).

5. Prolonged left median central conduction study (F-wave) of 34.2 ms (normal < 32 ms for individual < 72 inches, as was the case here). While prolonged, the prolonged latency (slowing) at or distal to the wrist, accounts for the noted increase in the central conduction study.

6. Abnormal EMG noted in two muscles, the left APB and left opponens pollicis (OP). Specific EMG findings included the following:

   a. Increased insertional activity in the left APB and left OP.

   b. Fibrillation potentials (1+) and positive sharp waves (2+) in the left APB and left OP. The amplitude of the fibrillation potentials observed were small (< 100 uV), and this size observation may be related to relative chronicity of the denervation observed.[10-11]

   c. With full voluntary activation, both the left APB and left OP demonstrated a screen fill reflective of dropped motor units during full voluntary contraction (75% screen fill).

All NCS and EMG results for the left ulnar nerve, left superficial radial nerve, and all other assessed EMG were unremarkable.

Collectively, the findings outlined above provide electrophysiological and clinical evidence of a severe distal left median neuropathy with slowing at or distal to the wrist (demyelination and axonal findings), consistent with a referring consult for left CTS. This leaves the question when talking to the patient or providing the referring practitioner. "What is a straightforward way to clearly communicate what these collective findings demonstrate?" A neurophysiological classification system is useful when engaging in these verbal and written communications.

The GEHS system,[19] like the Bland system,[17,18] is based on a thorough patient history and a scanning physical exam. A key difference in the GEHS system, is that it also examines EMG findings, so that axonal involvement can be documented and factored into the decision-making process in terms of severity (Table 1).

Presenting Results Based on the Neurophysiological Classification System: When writing the note for the referring provider, all of the abnormal findings identified

during the examination, to include the patient's subjective sensory issues, the demonstrated decreased sensation during the scanning physical exam, and all of the objective NCS/EMG were listed. These were then placed within the context of the GEHS classification system, which categorized this patient as having a 'severe' distal median neuropathy with slowing at or distal to the wrist (normal NCS proximal to the wrist). To guide both the health care provider and the patient to why this was a 'severe' CTS, the chart provided above was dropped into the note and the box that most closely represented the patient being examined with demonstrated CTS was both highlighted and asterisked. This chart then provides the basis from which a clear conversation can outline how the electrophysiological testing uses collaborative information to make a determination first of a specific problem (including portion of the nerve impacted), as well as severity of the underlying condition.

Potential Advantages of Neurophysiological Classification System Implementation: Using a system such as the GEHS Neurophysiological Classification System, provides a number of potential advantages for the individual performing electrophysiological testing. These advantages include the following:

1. Facilitate information overview of the findings to a patient, in a readily understood format that also allows the patient to understand the progression of symptoms from mild to severe.

2. Clarity of data and how an interpretation (in the above case, 'severe') is made, and supported for the referring provider.

3. Ease of recommendation of potential treatment to be offered, with ability to incorporate NCS, EMG, history, and any physical exam findings into a treatment recommendation.

4. Findings from this survey provide direct linkage between level of severity and the type of treatment being used by other clinicians.

Results

Of the 35 referring providers of NCS/EMG services for their patients with CTS contacted to participate in this study, 14 providers completed the online survey (40%). This included 12 physicians (MD), one osteopathic physician (DO), and one nurse practitioner (NP). All 14 providers had attained board certification (orthopaedics—nine; family practice—one; and other—four). Eight of the referring providers had greater than 20 years of clinical practice, one has practiced 16 to 20 years, two have practiced six to ten years, and one has practiced for one to five years.

Twelve of the referring providers (85.7%) were familiar with clinical electrophysiological classification systems for patients with CTS. Nine referring providers use a neurophysiological classification system (GEHS and Bland—six; GEHS only—two; alternate system—one). Five respondents do not use a neurophysiological classification system, two of which were not familiar with these classification systems. The nine providers who use a neurophysiological classification system for their patients with CTS found these systems useful in assessing patient prognosis, treatment planning, and communicating back to referral services.

The responses obtained demonstrated a clear linkage between the findings based on a neurophysiological classification system and the type of treatment ultimately provided to the patient. Using the electrophysiological data collected within these systems, the providers rank ordered the interventions for CTS with "1" being most preferable treatment approach and "6" least preferable treatment approach. Each classification system and its corresponding interventions for patients with CTS are as follows:

Mild (sensory only or sensory & motor): The most preferable treatment for mild classification was splinting (71.4%), followed by oral medication (16.7%), and injection (15.4%). The least preferable interventions for this classification was surgery (endoscopic and open) and physical therapy/occupational therapy (PT/OT) services.

Moderate: Again, the most preferable intervention for the moderate classification was splinting (61.5%). Surgery (open and endoscopic) was the second most preferable intervention (16.7%); followed by injection (15.4%), and oral medication (8.3%). Referral for PT/OT services was the least preferable intervention (33.3%).

Moderate/Severe: For this electrophysiological classification, splinting (38.5%), surgery (open; 30.8%), and surgery (endoscopic; 25%) were the interventions of choice. If the two surgery interventions were combined, 50% of the providers rated surgery as the top intervention for moderate/severe classification. Oral medication (0%) and PT/OT services (0%) were the least preferable interventions for patients with moderate/severe CTS.

Severe: Ten of the 14 providers stated surgery (open, 53.9% or endoscopic, 25%) was the most preferable intervention for patients with severe CTS. Splinting (16.7%) and injection (16.7%) were also included as interventions for this classification. Again, oral medication and

PT/OT services were the least preferable (0%) intervention for patients with severe CTS.

The data presented above clearly demonstrates that across the continuum of patients with CTS, the treatment approach varies based on severity. Determining severity of CTS is based on data that includes history, physical exam, electrophysiological testing, imaging, and past treatments. The referring providers were asked, within this context of treatment variability for different levels of CTS severity, at what level of CTS involvement do you typically select a surgical intervention? The providers indicated through the survey surgical intervention would occur at the moderate classification (42.9%) or at the moderate/severe (42.9%) classification. None of the providers stated surgical interventions would occur for patient with CTS in the very mild or mild classifications. The data demonstrated this was a clear point of distinction where the electrophysiological data directly assisted in the decision process for treatment that considered a surgical remedy.

The referring providers of EMG/NCS services were given the opportunity to provide any additional information that might be beneficial to the survey. One provider stated a patient with moderate findings of CTS who does repetitive work may be considered for a surgical intervention before a patient with moderate findings who does not perform repetitive work. Another provider said surgical intervention should be considered if a patient with CTS has failed conservative treatment, regardless of the electrophysiological classification. A provider commented the "best indicator" of a patient with severe CTS would be a distal motor latency of > 5.5 ms (at a distance of 8 cm, assessed over the abductor pollicis brevis muscle).

Discussion

Classification systems for patients with CTS reported in the literature are largely based on data from electrophysiological studies.[17-20, 23-24] Neurophysiological classification systems for patients with CTS provide health care practitioners an enhanced system of electrophysiological evaluation and grading scale. The first research question addressed in this study was determining if the referring providers were familiar with the Bland and GEHS neurophysiological classification system for patients with CTS. Eighty-five percent of the referring providers (12/14) were familiar with clinical electrophysiological classification systems for patients with CTS.

Another research question addressed in this study was assessing if referring providers used these neurophysiological classification systems for patients with CTS to determine interventions for these patients. Nine referring providers (64%) used a neurophysiological classification system (GEHS and Bland—six; GEHS only—two; alternate system—one). Five respondents (36%) did not use a neurophysiological classification system for patients with CTS, and two providers were not familiar with these classification systems. The nine providers who use a neurophysiological classification system for their patients with CTS found these systems useful in assessing patient prognosis, treatment planning, and communicating back to referral services.

The referring providers then rank ordered the interventions for each electrophysiological classification system of patients with CTS, with "1" being most preferable and "6" least preferable. All of the referring providers who participated in this study provided their interventions for each electrophysiological classification system for patients with CTS regardless if they were using the classification system or not.

The key findings from this review of interventions were three basic tiers of treatment, and these were based on the level of severity as outlined by the examined neurophysiological classification systems. These levels were as follows: Tier One: Patients identified by a system with documented CTS in the very mild or mild categories (either sensory findings only, or sensory and motor findings with only moderately prolonged latencies) were generally treated with splinting, followed by oral medication and injection. The least preferable option for this category of patients was surgery. Tier Two: Patients identified within a moderate category (more pronounced demyelination with latencies clearly prolonged compared to the contralateral side or a Table of Normal Values) were still splinted as a form of initial treatment. However, at this level of involvement, surgery (open and endoscopic) was the second most preferable intervention, followed by injection and oral medication. Tier Three: From the data analyzed in this study, surgery (open and endoscopic) and splinting were the interventions of choice for the moderate/severe and severe electrophysiological classifications.

Surgery, combining both endoscopic and open surgical approaches, was the preferred intervention for patients classified as having moderate/severe and severe levels of CTS, and was selected by 50% of participating providers. The data suggests this was a point of distinction where electrophysiological classification potentially influenced the decision process towards surgical intervention.

Another finding was regardless of the level of severity as identified by the neurophysiological classification

systems, the least preferable intervention option was PT and/or OT services. When conservative treatment was called for by the referring providers, generally Tier One and Tier Two, the conservative intervention for patients with CTS typically involved activity modification, wrist splints, anti-inflammatory or analgesic medications (or both), and occasionally injections of corticosteroids in the carpal tunnel.[25]

Table 1. Greathouse Ernst Hall Shaffer (GEHS) neurophysiological classification system for patients with carpal tunnel syndrome (CTS).

Grade	Nerve Conduction & Electromyography (EMG) Findings
Very Mild	Abnormal comparison study; e.g., prolonged comparison study between D4 median/ulnar DSLs; Normal EMG of the APB
Mild (sensory only)	Prolonged palmar and/or D2 DSLs Normal DML to APB and Normal EMG of the APB
Mild (sensory and motor)	Prolonged palmar and/or D2 DSLs Prolonged DML to APB < 5.0 ms, and normal EMG of the APB
Moderate	Prolonged or absent DSLs Prolonged DML to APB < 6.0 ms, and Normal EMG of the APB
Moderate/Severe	Prolonged or absent DSLs Prolonged DML to APB > 6.0 ms EMG – presence of abnormal spontaneous electrical activity in the APB; no decrease in interference pattern or abnormal MUP duration and amplitude of the APB
Severe**	Prolonged or absent DSLs Prolonged DML to APB > 7.0 ms EMG—presence of abnormal spontaneous electrical activity in the APB; decreased interference pattern of APB, may have abnormal duration and amplitude of motor unit potentials in the APB

Distal Sensory Latency (DSL); Distal Motor Latency: (DML); Electromyography (EMG); Abductor Pollicis Brevis (APB); Digit2 (index finger) (D2)

Patients with CTS who do not improve with conservative measures often receive surgical decompression of the carpal tunnel.[25-26] Approximately 250,000 to 300,000 carpal tunnel releases are performed annually in the US.[26] The carpal tunnel release surgery is reported to relieve symptoms in 70% to 90% of patients.[27-29]

Of the 35 referring providers of NCS/EMG services for their patient with CTS contacted to participate in this study, 14 providers completed the on-line survey (40%). A 40% to 50% return rate on survey research is common.[30-32] While a less than optimal return rate on survey research is common, a goal of all research of this type is to obtain the best possible response rate to have a more representative sample. To facilitate the best response rate possible, this survey was deployed on three occasions to the list of referring providers, and each subsequent follow-up included a request to participate in this survey research. Ideally, this research would have obtained survey rates of 60% (good response rate) to 70% of the sample pool (very good response rate).[33] The achieved response rate of 40% is a potential limitation of the study. The consistency of the responses, in terms of being able to aggregate treatment approaches based on the classification systems results, suggests the basic utility of the classification systems was demonstrated. Future research might consider selecting one classification system, training practitioners in how to use the system, and then assess its utility in communicating with patients and in assisting health care providers make decisions about optimal treatment for a patient. Additional longitudinal prospective research is also needed to assess the prognostic utility and correlation of various CTS classification systems with patient outcomes.

While the focus of this research was on assessing how neurophysiological classification systems are utilized in determining interventions for patients with CTS, there are other potential benefits from using one of these systems.[17-19] A key benefit is that a systems approach is readily understood by both patients and referring health care providers, and it is an ideal way to communicate the findings to both constituents. From the data presented previously, use or even knowledge of a classification system for CTS was not employed by 36% of the referring providers. The following case study is an example of how the GEHS system might be used during a patient care visit to share the findings with a patient, the referring care provider, as well as providing an abridged list of potential advantages to using a classification system.

Conclusion

The findings from this study suggest the vast majority of providers who took part in the survey were familiar with clinical electrophysiological classification systems for patients with CTS. In addition, nine of the 14 referring providers reported using a neurophysiological classification system (GEHS and Bland—six; GEHS only—two; alternate system—one) as part of their decision-making process. Finally, the most preferable treatments for the very mild and mild (sensory only; sensory and motor) classifications were splinting, followed by oral medication and injection. From the data analyzed in this study, splinting and surgery (open and endoscopic) were the interventions of choice for the moderate/severe and severe electrophysiological classifications.

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Authors

Greg Ernst is Associate Professor, Department of Physical Therapy, UT Health Science Center, San Antonio, TX, and Clinical Electrophysiologist, Hand Center of San Antonio, TX.

Scott W. Shaffer is Professor, Department of Physical Therapy, Texas State University, Round Rock, TX, and Clinical Electrophysiologist, Neurosurgical and Spine Clinic of Texas, San Antonio, TX.

John S. Halle is Professor, School of Physical Therapy, Belmont University, Nashville, TN, and Clinical Electrophysiologist, Department of Neurology, Blanchfield Army Community Hospital, Fort Campbell, KY.

David G. Greathouse is Director, Clinical Electrophysiology Services, Texas Physical Therapy Specialists, New Braunfels, TX, and Adjunct Professor, US Army-Baylor University Doctoral Program in Physical Therapy, Fort Sam Houston, TX.

An Analysis of Patient Experience and Adherence to Diabetes Medication among Military Health System Beneficiaries

Kimberley Marshall-Aiyelawo, PhD, USN MSC (ret)
Beatrice Abiero, PhD
Amanda Sackett, MPH
Sharon Beamer, AuD
Melissa Gliner, PhD
Terry McDavid
Janice Ellison, MA, USAF Nursing Services (ret)

Abstract

Objective: Few studies have investigated the relationship between patient experience and diabetes medication adherence among Military Health System (MHS) beneficiaries. We explored the link between patient experience survey ratings and adherence to diabetes medication. The hypothesis was that adherent patients would report better provider-patient experience than non-adherent patients.

Methods: Data included 2,599 patient surveys and pharmacy refill records. Adherence was determined using proportion of days covered (PDC) methodology where a patient must have had medications available 80% or more of the time during the observation period. Analysis involved multivariable logistic regression.

Results: Medication adherence was 60.2%. Regarding patient experience, those who were with their provider for 5 years or more had greater odds of adherence (OR 1.86[95%CI 1.19, 2.90]) Most of the patients in this study had high morbidity and high care utilization. Patient characteristics that significantly ($p<0.05$) differentiated adherent versus non-adherent patients were race, mental health status, multiple medication use, glycated hemoglobin (HbA1c) levels, and health utilization.

Conclusion: Two key factors of adherence that emerged from this study are that moderate (OR 2.54[95%CI 1.35, 4.75]) and elevated (OR 2.35[95%CI 1.29, 4.30]) HbA1c and patients with 7+ health care providers (OR 1.56[95%CI 1.06,2.29]) had greater odds of adherence. Findings suggest that ability to see provider when needed and provider continuity support adherence to treatment. The practice implications of this study are health practitioners can leverage patient experience and pharmacy data to identify patterns of adherence among patients in the MHS.

Keywords: patient experience, diabetes, medication adherence, CAHPS

Introduction

Diabetes has some of the lowest medication adherence rates, compared to other chronic conditions such as pulmonary and cardiovascular diseases.[1,2] Non-adherence is a key predictor of comorbidities[3] and emergency department visits resulting in substantial medical costs on a yearly basis.[4] Although non-adherence is common among patients with diabetes,[5] not all the mechanisms for explaining non-adherence are well understood. Studies have shown a lack of patient-provider relationship leads to poor adherence,[6,7] and a collaborative physician-patient framework is important in effective diabetes management, particularly with type 2 diabetes.[8,9] As a result, high patient satisfaction with provider communication is likely an indication of a more collaborative patient-provider relationship, which in turn, may translate to adherence of treatment regimens.

Pioneer studies in adherence suggest the burden of adhering to treatment regimens is on the patient. However, patient experience and provider-patient communication play an essential role in adherence.[6,10] A cross-sectional study assessed patients perception of being "known as a person" by their provider was significantly associated with adherence to treatment regimens among 1,743

patients with HIV;[11] another study also found significant associations between quality patient-provider relationship and adherence to hypertension medication.[12] Better patient experience and patient-centered care directly reduces health costs, improves clinical outcomes, patient safety, and medication adherence.[13] Strong patient-provider communication plays an important role in the consultation process of care regarding goals and treatment plans. The overall patient experience is not just determined by the time the patient spends in a facility but by many other factors such as the concern, empathy, quality of communication, and continuity of care they receive. In this study, we are interested in how the role of patient experience, provider communication, and patient characteristics predict adherence to diabetes medication.

Current research is limited on understanding the role of patient experience on diabetes medication adherence among military active duty and non-active duty service members and their families. While military service members have a lower prevalence of diabetes compared to the general population, overall trends in type 2 diabetes have increased over the past few decades.[14,15] A recent report estimated the following crude overall incident rates (per 100,000 person years) of type 2 diabetes between 2008-2018: 71.6 for active component and 63.8 for reserve component.[16] Military personnel and their families are a generally understudied demographic, whose mechanisms of risk are still poorly documented or understood. Furthermore for the military, maintaining a healthy population and managing existing diabetes conditions is crucial for supporting medical readiness given that certain health issues can affect individual readiness to deploy or fitness for active duty.[17]

Pharmacy records, which include the timing of medication orders and subsequent refills, are used for measuring adherence.[18-20] The preferred method for measuring adherence for chronic drug therapies is based on Proportion Days Covered (PDC), which is based on a methodology sanctioned by the Pharmacy Quality Alliance (PQA)[21] and used by Centers for Medicare and Medicaid Service (CMS) to assign star ratings for Medicare Part D programs.[22] The patient must have at least a 120-day supply within a targeted drug class during the observation period. For this study, the observation period is a year within the outpatient encounter. For example, if the patient had a visit in June 2016, the observation period would be through June 2017. Typically, patients with diabetes take more than one medication. PDC is considered a good method for capturing adherence among patients with diabetes since this method also captures medication regimens for multiple medication use.[23]

In this study, we consider the effect of patient experience with provider communication including—attentiveness, respect, and knowledge of patient medical history—and provider rating on diabetes medication adherence using measures from the Clinician and Group Consumer Assessment of Healthcare Providers (CG-CAHPS) survey. We also account for multiple medication use and length of time with provider. Here we build upon insights by Matthews et al,[10] which focused on the important role of provider communication on patient adherence through a qualitative study that investigated diabetes management among women. Our approach is quantitative and looks at both genders receiving care within the Military Health System (MHS). We also examine if there are differences by race and Hispanic ethnicity.

Methods

Research Design: The Joint Outpatient Experience Survey CG-CAHPS (JOES-C) reports on the experiences of outpatient beneficiaries receiving care from military treatment facilities (MTFs) in the MHS. The JOES-C program uses the CG-CAHPS adult Version 3.0 protocol and survey instrument where patients report on their most recent outpatient experience with a given provider. The recall period for the survey is 6 months. The data for this study includes MTF patients with outpatient visits from June 2016 through December 2016. This includes active duty, active duty family, retirees, and retiree family member beneficiaries. Under the CG-CAHPS protocol, the study measures access to care, provider communication and courtesy, effectiveness of clerks/receptionists, perceptions of the MHS, and overall satisfaction with provider, healthcare, and TRICARE plan. We focused on CG-CAHPS measures of provider communication and provider's knowledge of patient's medical history. In addition, we included the patient's length of time with the provider, whether the provider was their usual provider, and if the patient indicated they were able to see their provider when needed. This study was approved under the Defense Health Agency Internal Review Board.

The PDC measure is an administrative measure coded into registries in the MHS Population Health Portal. The algorithms that produce the PDC values are validated measures procured from Johns Hopkins as part of the Adjusted Clinician Group (ACG) analytics package. PDC in the ACG data repository provides a rolling year-long snapshot of adherence and is calculated monthly. If a patient met diagnostic and treatment criteria for diabetes, then the ACG system calculated a PDC during that period. For the PDC measure, adherence is when medications are available for 80% or more of the time during

the observation period.[24] The ACG includes 7 drug classes for diabetes: insulins, meglitinides, antidiabetic agents, non-sulfonylureas, antihyperglycemic agents, sulfonylureas, and thiazolidinediones. Metformin, a first line drug for managing type 2 diabetes, was included in the "Non-sulfonylureas" drug class.

The initial JOES-C sample was 11,279, which included patients taking medications for various disease conditions. Among the 11,279 patients, there were 2,942 taking diabetes medications, with 343 patients missing a PDC value. Medication adherence was not assessed under certain conditions. For example, a PDC value was not calculated when the prescribed active ingredient fell within a drug class used to identify the condition is present (e.g., short-acting insulins) and was not eligible for adherence calculations. Adherence was not assessed if the patient did not have at least 120-day supply within a targeted drug class during the observation period. Finally, in cases where the patient had 2 prescriptions within the same drug class but not for the same active ingredient, a PDC value was not generated. The final matched sample included in the study was 2,599 patients.

The guiding hypothesis in this study is positive patient experience (i.e., provider communication, provider knowledge of patient's medical history, etc.), which corresponds with better adherence outcomes. Additionally, there are known sociodemographic and health risk factors associated with diabetes, which were also accounted for in this study. To test whether baseline patient characteristics and patients who reported better patient experience were more likely to have better adherence, we needed to collect PDC data in the 365-day period following the date of their JOES-C encounter. Therefore, medication adherence data was captured from June 2016 through December 2017. In this study, we averaged PDC values if a patient was taking more than one diabetes drug and categorized them as adherent or not based on the 80% threshold as recommended by PQA. There were 1,564 adherent patients, of whom 867 were taking more than one diabetes drug, and 1,035 non-adherent patients, of whom 526 were taking more than one diabetes drug.

Table 1. Patient demographics by diabetes medication adherence status.

	Not Adherent (n=1,035, 39.8%)		Adherent (n=1,564, 60.2%)	
	Weighted %	95% CI	Weighted %	95% CI
Age Group				
18-34	0.7	(0.00,0.01)	0.6	(0.00,0.01)
35-44	2.6	(0.02,0.04)	2.0	(0.01,0.03)
45-64	56.4	(0.54,0.59)	52.7	(0.51,0.55)
65+	40.2	(0.38,0.43)	44.7	(0.43,0.47)
Beneficiary Category				
Active Duty	2.1	(0.01,0.03)	1.6	(0.01,0.02)
Active Duty Family	4.8	(0.04,0.06)	4.2	(0.03,0.05)
Retirees and Family Members <65	21.5	(0.19,0.24)	18.8	(0.17,0.20)
Retirees and Family Members 65+	71.6	(0.69,0.74)	75.5	(0.74,0.77)
Gender				
Male	56.7	(0.54,0.59)	59.1	(0.57,0.61)
Female	43.3	(0.41,0.46)	40.9	(0.39,0.43)
Race & Hispanic Ethnicity*				
White Non-Hispanic	53.7	(0.51,0.56)	57.6	(0.56,0.60)
Black Non-Hispanic	18.7	(0.17,0.21)	15.0	(0.14,0.17)
Asian, American Indian, Pacific Islander Non-Hispanic	14.3	(0.13,0.16)	15.8	(0.14,0.17)
Hispanic	12.2	(0.10,0.14)	10.2	(0.09,0.12)
2+races Non-Hispanic	1.1	(0.01,0.02)	1.4	(0.01,0.02)
Health Status				
Excellent/Very Good	21.2	(0.19,0.23)	24.2	(0.23,0.26)
Good	49.6	(0.47,0.52)	49.1	(0.47,0.51)
Fair/Poor	29.2	(0.27,0.32)	26.6	(0.25,0.28)
Mental Health Status*				
Excellent/Very Good	67.1	(0.64,0.70)	62.7	(0.61,0.65)
Good	21.5	(0.19,0.24)	25.7	(0.24,0.28)
Fair/Poor	11.5	(0.10,0.13)	11.6	(0.10,0.13)
Education				
Less than high school	3.7	(0.03,0.05)	4.2	(0.03,0.05)
High school graduate or GED	20.8	(0.19,0.23)	23.5	(0.22,0.25)
Some college or 2-year degree	43.1	(0.40,0.46)	40.1	(0.38,0.42)
4-year college graduate	15.1	(0.13,0.17)	13.7	(0.12,0.15)
More than 4-year college degree	17.3	(0.15,0.19)	18.4	(0.17,0.20)

**Indicates statistical significance at P <0.05. Chi-square test was used to analyze remaining measures.*

Independent Variables: The baseline patient sociodemographic characteristics examined are age, beneficiary category, gender, race and Hispanic ethnicity, self-reported health status, self-reported mental health status, and education (Table 1). Age was categorized into four groups: 18-34, 35-45, 45-64, and 65 and older. Beneficiary category distinguished active duty, active duty family members, retirees and family members under the age of 65, and retirees and family members over the age of 65. Race and Hispanic ethnicity categories included White non-Hispanic, Black non-Hispanic, Asian, American Indian, Pacific Islander, Hispanic, and 2+races non-Hispanic. Self-reported health and mental health status were categorized as Excellent/Very Good, Good, Fair/Poor.

Table 2. Patient experience and health characteristics by diabetes medication adherence status.

	Not Adherent (n=1,035, 39.8%)		Adherent (n=1,564, 60.2%)	
	Weighted % or Mean	95% CI or SD	Weighted % or Mean	95% CI or SD
Mean Provider Communication Composite	(0.84)	0.31	(0.85)	.31
Mean Provider Rating	(9.11)	1.57	(9.19)	1.52
Provider Know Medical History				
Always	25.6	(0.23,0.28)	25.7	(0.24,0.28)
Usually, Sometimes, Never	74.4	(0.72,0.77)	74.3	(0.72,0.76)
Length of Time with Provider*				
Less than 6 months	40.5	(0.38,0.43)	40.9	(0.39,0.43)
At least 6 months but less than 1 year	16.3	(0.14,0.18)	12.6	(0.11,0.14)
At least 1 year but less than 3 years	24.7	(0.22,0.27)	24.3	(0.23,0.26)
At least 3 years but less than 5 years	9.8	(0.08,0.12)	10.6	(0.09,0.12)
5 years or more	8.7	(0.07,0.10)	11.6	(0.10,0.13)
Usual Provider*				
No	46.4	(0.44,0.49)	41.8	(0.40,0.44)
Yes	53.6	(0.51,0.56)	58.2	(0.56,0.60)
See Provider When Needed*				
Strongly disagree	3.8	(0.03,0.05)	3.1	(0.02,0.05)
Somewhat disagree	5.2	(0.04,0.07)	6.2	(0.04,0.09)
Neither agree nor disagree	5.1	(0.04,0.07)	10.1	(0.08,0.13)
Somewhat agree	30.0	(0.27,0.33)	26.9	(0.23,0.31)
Strongly agree	55.9	(0.52,0.59)	53.8	(0.49,0.58)
Multiple Medication Use (Any)*				
1 drug	2.5	(0.02,0.04)	1.2	(0.01,0.02)
2 drugs	9.5	(0.08,0.11)	7.3	(0.06,0.08)
3 drugs	14.6	(0.13,0.17)	13.3	(0.12,0.15)
4 drugs	16.4	(0.15,0.19)	16.1	(0.15,0.18)
5+ drugs	56.9	(0.54,0.59)	62.1	(0.60,0.64)
Multiple Diabetes Medication Use*				
Only 1 Diabetes Drug	25.3	(0.20,0.31)	13.6	(0.11,0.17)
Multiple Diabetes Drugs	74.7	(0.69,0.80)	86.4	(0.83,0.89)
HbA1c After Encounter*				
Normal (< 5.7%)	6.7	(0.05,0.08)	4.3	(0.03,0.05)
Moderate (5.8-6.4%)	23.2	(0.21,0.26)	23.9	(0.22,0.26)
Elevated (>6.5%)	70.1	(0.67,0.73)	71.8	(0.70,0.74)
Number of Unique Providers Seen*				
<3	13.4	(0.12,0.15)	17.2	(0.16,0.19)
4-6	27.8	(0.25,0.30)	29.6	(0.28,0.32)
7-9	23.0	(0.21,0.25)	25.3	(0.24,0.27)
>10	35.9	(0.33,0.38)	27.9	(0.26,0.30)
Frailty				
No	80.3	(0.78,0.82)	81.7	(0.80,0.83)
Yes	19.7	(0.18,0.22)	18.3	(0.17,0.20)
Resource Utilization Band				
Healthy/Low Morbidity	0.3	(0.00, 0.01)	0.3	(0.00, 0.01)
Moderate Morbidity	18.8	(0.17, 0.21)	24.7	(0.23, 0.26)
High Morbidity	41.0	(0.38, 0.44)	43.1	(0.41, 0.45)
Very High Morbidity	39.9	(0.37, 0.43)	31.9	(0.30, 0.34)

Student's t test was used to analyze mean communication and provider measures. Chi-square test was used to analyze remaining measures.
**Indicates statistical significance at P <0.05.*

The patient experience and health variables are detailed in Table 2. There are 4 provider communication CG-CAHPS questions averaged into a composite measure for this study. Correlation analyses conducted during exploratory analysis found high collinearity among these measures

providing support for combining these items. The questions asked about the frequency in which the provider explained things in an easy-to-understand way, listened carefully, showed respect for what the patient had to say, and spent enough time with the patient. The response options are always, usually, sometimes, never. Each provider communication measure was dichotomized to 1=always, and 0=usually; sometimes, never then averaged for each patient. A provider rating question was also included: "Using any number from 0 to 10, where 0 is the worst provider possible and 10 is the best provider possible, what number would you use to rate this provider?" Given experience scores tend to be highly positively skewed among the study sample, this variable was mean centered. Patient's perception of provider's knowledge of their history was dichotomized to 1=always, and 0= usually, sometimes, never. Additional variables associated with the patient's relationship with the provider was the length of time spent seeing the provider (less than 6 months to 5 years or more), whether the provider was their usual provider, and whether the patient perceived they could see the provider when needed.

Table 3. Predicting adherence to diabetes medications—unadjusted logistic regression results.

	Unadjusted Odds Ratio	SE	*P*	95% CI
Mean Provider Communication Composite	1.06	0.110	0.57	(0.87, 1.29)
Mean Provider Rating	1.03	0.021	0.12	(0.99, 1.08)
Provider Know Medical History (Ref. Always)				
Usually, Sometimes, Never	1.06	0.077	0.46	(0.92, 1.22)
Length of Time with Provider (Ref. Less than 6 months)				
At least 6 months but less than 1 year	0.85	0.080	0.08	(0.70, 1.02)
At least 1 year but less than 3 years	1.01	0.081	0.88	(0.87, 1.18)
At least 3 years but less than 5 years	1.05	0.118	0.69	(0.84, 1.30)
5 years or more*	1.28	0.147	0.03	(1.02, 1.60)
Usual Provider (Ref. No)				
Yes*	1.16	0.075	0.02	(1.02, 1.32)
Able to See Provider When Needed (Ref. Strongly Disagree)				
Somewhat disagree	1.39	0.512	0.37	(0.68, 2.86)
Neither agree nor disagree*	2.32	0.847	0.02	(1.14, 4.75)
Somewhat agree	1.28	0.400	0.44	(0.69, 2.36)
Strongly agree	1.34	0.408	0.34	(0.74, 2.43)
Multiple Drug Use (Ref. 1 drug)				
2 drugs	1.46	0.375	0.15	(0.88, 2.41)
3 drugs*	1.75	0.433	0.03	(1.07, 2.84)
4 drugs*	1.80	0.445	0.02	(1.11, 2.93)
5+ drugs*	2.13	0.508	0.00	(1.34, 3.40)
Diabetes Drug Count (Ref. Only 1 Diabetes Drug)				
Multiple Diabetes Drugs*	1.77	0.318	0.00	(1.24, 2.52)
Age Group (Ref 18-34)				
35-44	0.86	0.402	0.74	(0.34, 2.15)
45-64	0.12	0.475	0.78	(0.49, 2.57)
65+	1.37	0.580	0.46	0.60, 3.14)
Beneficiary Category (Ref. Active Duty)				
Active Duty Family	1.12	0.356	0.71	(0.60, 2.09)
Retirees and Family Members <65	1.01	0.279	0.98	(0.58, 1.73)
Retirees and Family Members 65+	1.39	0.376	0.23	(0.82, 2.36)
Gender (Ref. Male)				
Female	0.89	0.540	0.06	(0.79, 1.00)
Race & Hispanic Ethnicity (Ref. White Non-Hispanic)				
Black Non-Hispanic*	0.83	0.072	0.03	(0.70, 0.98)
Asian, American Indian, Pacific Islander Non-Hispanic	0.97	0.087	0.73	(0.81, 1.15)
Hispanic*	0.80	0.818	0.03	(0.66, 0.98)
2+races Non-Hispanic	0.94	0.244	0.82	(0.57, 1.56)
Health Status (Ref. Excellent/Very Good)				
Good	1.02	0.077	0.82	(0.88, 1.18)
Fair/Poor	0.91	0.078	0.28	(0.77, 1.08)
Mental Health Status (Ref. Excellent/Very Good)				
Good*	1.26	0.092	0.00	(1.09, 1.46)
Fair/Poor	1.08	0.019	0.42	(0.89, 1.32)
Educational Attainment (Ref Less than high school)				
High school graduate or GED	0.98	0.159	0.92	(0.72, 1.35)
Some college or 2-year degree	0.95	0.148	0.73	(0.70, 1.29)
4-year college graduate	0.93	0.158	0.67	(0.70, 1.30)
More than 4-year college degree	0.97	0.160	0.83	(0.70, 1.34)
HbA1c After Encounter (Ref. Normal <5.7%)				
Moderate (5.8-6.4%)*	1.43	0.223	0.02	(1.06, 1.94)
Elevated (>6.5%)*	1.43	0.208	0.01	(1.08, 1.91)
Resource Utilization Band (Ref. Healthy/Low Morbidity)				
Moderate Morbidity	1.05	0.663	0.94	(0.31, 3.62)
High Morbidity	0.96	0.602	0.95	(0.28, 3.29)
Very High Morbidity	0.79	0.497	0.71	(0.23, 2.71)
Unique Provider Count (Ref. <3)				
4-6	0.90	0.081	0.24	(0.75, 1.07)
7-9	1.04	0.100	0.68	(0.86, 1.25)
>10	0.80	0.072	0.01	(0.66, 0.94)
Frailty (Ref. No)				
Yes	1.00	0.080	0.96	(0.86, 1.15)

**Indicates statistical significance at P <0.05.*

Several patient baseline health characteristics were considered. We calculated whether patients were taking more than one medication of any kind as well is if they were taking more than one diabetes medication specifically. HbA1c or average blood glucose was categorized based on clinical guidelines from the American Diabetes Association—normal (<5.7%), moderate/prediabetic (5.8-6.4%), and elevated/diagnosed diabetic (>6.5%). Care utilization (high versus low) was determined based on the number of unique eligible providers (0 to more than 10) providing outpatient care to the patient for any condition over the measurement period. The frailty flag is an MHS marker of health status indicating whether a beneficiary had a diagnosis of a medical condition associated with frailty. The resource utilization band (RUB) score was an administrative indicator of health status that stratifies the patient population into Healthy/Low Morbidity, Moderate Morbidity, High Morbidity, and Very High Morbidity. This measure is typically used to show changing morbidity patterns within a population and expected resource use in the coming year as determined by the ACG system.

Statistical Analysis: Statistical analyses included chi-square tests of association and t tests to compare baseline patient demographic, health, and experience measures by adherence status. Additional exploratory and correlation analyses were done before conducting logistic regression analysis. Logistic regression analysis was used to examine the bivariate relationship between each of the measures in Table 1 with the outcome variable adherence to diabetes medication. Significant measures

Table 4. Predicting adherence to diabetes medications—adjusted logistic regression results.

	Adjusted Odds Ratio	SE	*P*	95% CI
Mean Provider Communication Composite *	0.44	0.145	0.01	(0.23, 0.84)
Mean Provider Rating	1.07	0.056	0.22	(0.96, 1.18)
Provider Know Medical History (Ref. Always)				
Usually, Sometimes, Never*	2.04	0.435	0.00	(1.34, 3.10)
Length of Time with Provider (Ref. Less than 6 months)				
At least 6 months but less than 1 year	1.19	0.208	0.31	(0.85, 1.68)
At least 1 year but less than 3 years	1.27	0.210	0.14	(0.92, 1.76)
At least 3 years but less than 5 years	0.90	0.218	0.67	(0.56, 1.45)
5 years or more*	1.86	0.423	0.01	(1.19, 2.90)
Usual Provider (Ref. No)				
Yes	1.04	0.142	0.75	(0.80, 1.36)
Able to See Provider When Needed (Ref. Strongly Disagree)				
Somewhat disagree	1.33	0.586	0.51	(0.56, 3.15)
Neither agree nor disagree*	2.97	1.276	0.01	(1.28, 6.90)
Somewhat agree	1.22	0.444	0.59	(0.60, 2.49)
Strongly agree	1.04	0.372	0.92	(0.51, 2.10)
Multiple Drug Use (Ref. 1 drug)				
2 drugs	1.46	0.842	0.51	(0.47, 4.52)
3 drugs	1.52	0.851	0.45	(0.51, 4.55)
4 drugs	2.51	1.399	0.10	(0.84, 7.48)
5+ drugs	1.74	0.952	0.31	(0.60, 5.08)
Age Group (Ref. 18-34)				
35-44	0.87	1.071	0.91	(0.08, 9.67)
45-64	1.10	1.320	0.93	(0.11, 11.50)
65+	1.08	1.302	0.95	(0.10, 11.49)
Beneficiary Category (Ref. Active Duty)				
Active Duty Family	0.63	0.413	0.48	(0.17, 2.28)
Retirees and Family Members <65	0.64	0.367	0.43	(0.20, 1.97)
Retirees and Family Members 65+	0.64	0.357	0.42	(0.21, 1.91)
Gender (Ref. Male)				
Female	0.96	0.159	0.79	(0.69, 1.32)
Race & Hispanic Ethnicity (Ref. White Non-Hispanic)				
Black Non-Hispanic	0.76	0.140	0.14	(0.53, 1.09)
Asian, American Indian, Pacific Islander Non-Hispanic	1.24	0.226	0.24	(0.87, 1.77)
Hispanic	0.94	0.185	0.75	(0.64, 1.38)
2+races Non-Hispanic	0.91	0.436	0.84	(0.36, 2.32)
Mental Health Status (Ref. Excellent/Very Good)				
Good	1.22	0.177	0.17	(0.10, 1.62)
Fair/Poor	0.75	0.175	0.22	(0.48, 1.19)
Educational Attainment (Ref. Less than high school)				
High school graduate or GED	1.04	0.415	0.92	(0.48, 2.27)
Some college or 2-year degree	1.60	0.627	0.23	(0.74, 3.45)
4-year college graduate	2.16	0.884	0.06	(0.97, 4.81)
More than 4-year college degree	1.75	0.719	0.17	(0.79, 3.92)
HbA1c After Encounter (Ref Normal <5.7%)				
Moderate (5.8-6.4%)*	2.54	0.813	0.00	(1.35, 4.75)
Elevated (>6.5%)*	2.35	0.723	0.01	(1.29, 4.30)
Unique Provider Count (Ref. <3)				
4-6	1.24	0.240	0.28	(0.84, 1.81)
7-9*	1.56	0.306	0.02	(1.06, 2.29)
>10*	1.46	0.284	0.05	(1.00, 2.14)

**Indicates statistical significance at P <0.05. N=1,377.*

and factors theorized to impact diabetes medication adherence were included in a final multivariable logistic regression model in a stepwise fashion to adjust for potential confounding variables identified in the initial exploratory analysis. Listwise deletion was employed for any patients missing variables for the final logistic model. All analyses were weighted to account for the survey design's nonproportional sampling as well as survey nonresponse. Regression diagnostics included examining covariates for multicollinearity based on variance inflation factor and tolerance values.

Results

Table 1 and Table 2 summarize patient demographic and health characteristics. The proportion of patients who were adherent was 60.2% and 39.8% for those who were not adherent. Results from our univariate comparisons of patients by adherence status indicates that non-adherent patients were significantly (P<0.05) more likely to be non-White compared to adherent patients—46.3% compared to 42.4% respectively, have greater incidence of multiple medication use, have very high morbidity, and have 10 or more unique providers. Results in Table 2 show adherent patients were significantly more likely to take more than five medications by five percentage points, and multiple diabetes drugs by more than 10 percentage points. Additionally, adherent patients were more likely to be with their provider for at least 3 years or longer and more likely to report that the provider on the JOES-C survey was their usual provider.

Table 3 includes unadjusted log odds from bivariate logistic regressions where each variable was tested separately to predict adherence. Usual provider yes, neutral stance (Neither agree nor disagree) on being able to see provider when needed, multiple medication use (any type of medication), multiple diabetes drug use, Black non-Hispanic, and Hispanic membership, good mental health status, and moderated and elevated HbA1c significantly (P<0.05) predicted greater odds of adherence with the exception of Black non-Hispanic and Hispanic membership. Notably, those taking 5 or more medications (any type) had 2.13 greater odds [95%CI 1.34, 3.40] of adherence compared to those taking one medication.

Table 4 includes the final variables included in the multivariable logistic regression model which adjusted for any potential confounding. Provider communication and provider knowledge of medical history became significant (P<0.05). Those with a higher provider communication mean had 0.44 fewer odds of adherence [95%CI 0.23, 0.84]. Patients indicating their provider usually, sometimes, or never knew their medical history had 2.04 greater odds [95%CI 1.34, 3.10] of adherence compared to those who strongly disagreed. The magnitude in odds of adherence increased and remained significant for patients who spent 5 or more years with their provider, for patients perceiving that they neither agreed or disagreed that they were able to see provider when

needed, and patients with moderate and elevated HbA1c. Usual provider, multiple medication use, Black non-Hispanic and Hispanic membership, and mental health status were no longer significant. Finally, those with 7-9 or 10 or more unique providers had approximately 1.56 and [95%CI 1.06, 2.29] and 1.46 [95%CI 1.00, 2.14], respectively, greater odds of adherence compared to those with one provider.

Discussion

The growing burden and cost of diabetes make it imperative for health researchers and practitioners to understand and develop better strategies for improving medication adherence to promote diabetes management that can be implemented in the MHS as well as civilian healthcare systems. In this study, we examined the relationship between patient experience and adherence to diabetes medication among a sample of MHS beneficiaries who had completed the JOES-C survey about an outpatient visit. Identifying and understanding opportunities to improve treatment adherence for diabetes represent key research areas particularly for patients in the MHS. In our study, we found the incidence of non-adherence to be 39.8%. Research suggests that 40%[9] to 50%[20] of patients fail to adhere to treatment regimens.

Our study found a relationship between CG-CAHPS provider communication composite score and adherence but not as hypothesized. Adherence was associated with a lower mean provider communication score rather than a higher score. However, there may be some qualitative aspect of the patient-provider communication not addressed in the measure, such as developing a collaborative relationship resulting in shared understanding of health goals, to establish diabetes management. We did note patients who indicated that the provider knew the patient's medical history only some of the time or never had 2.04 ($P<0.05$) greater of odds of being adherent compared to those who indicated the provider always knew their medical history. This result was also unexpected. Additionally, for those who were neutral about their ability to see their provider when needed had 2.97 ($P<0.05$) greater of odds of adherence compared to those strongly disagreeing they were able to see their provider when needed. Although findings were not significant for those indicating they agreed or strongly agreed they were able to see their provider, the odds of adherence for these patients was still greater compared to those strongly disagreeing they were unable to see their provider when needed.

Adequate and timely access to care is critical in maintaining the health of patients,[25] particularly those managing chronic conditions such as diabetes. Tenure with provider is a factor in continuity of care. Our descriptive findings showed statistically significantly greater proportions of adherent patients who had been with their provider for 3 years or more. Individuals who reported being with their provider for 5 years or more (after controlling for other factors) had 1.86 greater odds of being adherent compared to those who were with their provider for less than 6 months. It is important to note active duty members were more likely to have 10 or more providers. This is likely due to the nature of rotations/deployments and multiple appointments needed for medical readiness requirements. Additionally, it is not uncommon for providers to rotate within the MHS as well because of their own active duty status. Regarding patient characteristics we did not find significant differences by age, gender, race/Hispanic ethnicity, or education in the final model. Overall, the key significant predictors of adherence found in our study that underscore adherence are HbA1c levels, after the JOES-C encounter and the patient's number of unique providers.

Our study found those with moderate and elevated HbA1c levels had 2.54 and 2.35 greater odds ($P<0.05$) of adherence compared to those with normal levels. A recent study of Air Force personnel with diabetes found the service members experienced statistically improved HbA1c levels (<7%) post deployment compared to the 3 months before their deployment.[17] The investigators discussed that well-managed diabetes prior to deployment was critical and its effect remained after deployment and may have even improved HbA1c levels. Our findings suggest those with elevated HbA1c levels may be more accustomed to routinely adhering to their medications. However, HbA1c is just one measure of diabetes management. When communicating with patients, providers need to also take into account the relationship between adherence to antihyperglycemic medication and attainment of low HbA1c levels1 as failure to achieve low HbA1c level has also been associated with depression in type 1 but not type 2 diabetes.[26] There has also been a move away from using HbA1c as a measure of glycemic control, focusing on the "patient rather than the number," and redefining the stringency on HbA1c monitoring.[27]

Patients in this study were more likely to have very good to excellent mental health status for both the adherent and non-adherent groups. In the unadjusted model, mental health status was a significant predictor of adherence. Those with fair/poor mental health had 1.08 greater odds of adherence, and those with good mental health status had 1.26 greater odds of adherence. After accounting for the other variables in the adjusted model, the effect was no longer significant. However, the impact of depression and other mental illnesses on adherence behaviors

should be considered[2,26] in managing diabetic patients. Patients experiencing both depression and diabetes may have low adherence rates and should be monitored closely in order to achieve optimal glycemic control,[2] particularly patients older than 65.[5] Providers' communications toward patients should reflect sensitivity to patients' mental health status and understanding that no single HbA1c will be appropriate for every patient.

A more general focus on patient self-care is a common approach of diabetes management. More than 95% of diabetes care is done by the patient;[8] therefore, the patient must account for their diabetes management in the context of other life priorities, which can be influenced by environmental factors such as regional differences, household wealth and income, as well as accessibility and continuity of care. As a result, providers do not have much control over the patient's decisions about their care. Funnell and Anderson discredit concepts such as compliance and describe the notion of noncompliance as the patient and provider "working towards different goals."[8] The patient and provider should instead collaborate, and the patient, who is responsible for their own care and management, should set the goals since patients have the best knowledge of their lives and behaviors. Providers need to recognize the patient's expertise in the collaboration and work towards helping the patient achieve their goals. Glasgow and Anderson also recommend focusing on the patient's ability to "self-manage" their chronic health condition and identifying the behaviors that assist with self-management or self-care.[28]

Our study includes some limitations. Medication adherence measures based on pharmacy claims represent and quantify the degree of medication availability for a patient and do not capture all dimensions of adherence. The reasons why a patient may or may not take a medication are varied and complex. Here, we did not account for other contextual factors that have been cited as barriers for adherence including costs of medication;[5] health literacy;[29] lifestyle, nutrition, economic and social challenges;[30] and family support. One assumption of the PDC method is a patient filling a prescription corresponds with adherence; however, there are cases where patients fill prescriptions but do not take the medication or take it correctly. Regardless, PDC is still considered a validated measure for capturing adherence. Finally, our findings only account for patients who filled medications in the MHS and does not capture refills, which could have been made outside of the MHS.

Since the patient-provider visit is often the only time for the provider to discuss treatment and adherence options, it is critical to provide sufficient time for an honest discussion with patients about their treatment plan and daily adherence challenges.[31] With most diabetic treatment being conducted at home by the patient, emphasis must be placed on creating the time and space for a strong patient-provider relationship grounded in shared decision making. Effective and clear communication with the provider will enable a holistic plan to maintain the patient's medication adherence. The plan should include discussion of family or other support mechanisms to the treatment program.[32] This study provides context for characteristics that impact adherence to diabetes drugs in the MHS.

This study demonstrated utilizing both patient experience and pharmacy claims data can help contextualize and identify factors that impact diabetes medication adherence. Specifically, integrated data sources allow for a more comprehensive understanding of the demographic differences and risks in adhering to diabetes medication regimens. Practitioners, health educators, and researchers should leverage these data sources to understand the pattern of adherence. Additionally, ensuring patients have provider continuity at the onset of treatment and collaborative relationships with their providers will maximize the potential for medication adherence. It is important for all patients, especially those who are non-adherent, to emphasize education, counseling and other health activation modes in order to empower them in their care decisions and relationship with their provider. For the active duty members, in particular, non-adherence could significantly impact their medical readiness. With patient-centered care and quality patient-provider relationships in place greater outcomes in diabetes care can be achieved.

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Authors

Kimberley Marshall-Aiyelawo is with Defense Health Agency, Falls Church, VA.

Beatrice Abiero is with Ipsos Public Affairs, Washington DC.

Amanda Sackett is with Ipsos Public Affairs, Washington DC.

Sharon Beamer is with US Navy, Bureau of Medicine and Surgery, Falls Church, VA.

Melissa Gliner is with Defense Health Agency, Falls Church, VA.

Terry McDavid is with US Army, Office of the Surgeon General, Falls Church, VA.

Janice Ellison is with Patient Experience and Satisfaction Team Air Force Medical Readiness Agency (AFMRA), JBSA Lackland, TX.

The Epistemic Fallacy: Unintended Consequences of Empirically Treating (Clinically Diagnosed) Chronic Lyme Disease in a Soldier

LTC Vanessa R. Melanson, PhD, M(ASCP)CM
CDT Kalei A. Hering
James L. Reilly, MEd
1LT (ret) Joseph M. Frullaney
LTC(P) Jason C. Barnhill, PhD, M(ASCP)CM

Abstract

We document a military patient presenting with a diffuse set of symptoms suggestive of chronic Lyme disease (CLD) and the subsequent empiric treatment and health complications arising therein. The lay medical community, spurred by the internet, has ascribed these diffuse symptoms to various illnesses including CLD without confirmatory serological evidence of any underlying disease. With a growing community of patient advocates, CLD has become an illness with broad and highly generalized list of clinical symptoms and an absence of agreed-upon confirmatory laboratory tests. Further complicating matters, diagnostic criteria and treatment protocols differ between the Infectious Diseases Society of America and the International Lyme and Associated Diseases Society guidelines. Clinicians also face serious challenges in diagnosing and treating patients who present with generalized symptoms and close to 50 diagnostic tests for Lyme disease available in North America. Further complicating the picture for military patients seeking medical confirmation of a disease and resolution of their symptoms, medical fitness boards use putative diagnoses as prima faciae evidence in disability. Here a military patient with a long list of complaints that defy any clear or easy diagnosis and treatment is discussed. However, these symptoms taken together with selectively summed notes in the medical record in the absence of convincing and clear laboratory confirmation are suggestive of CLD and its complications, but no resolution was ultimately reached. With the presumptive determination of a medical disability due to CLD by the medical board, the medical dismissal of this service member from active duty occurred.

Introduction

Patients with a variety of debilitating symptoms, but without clear diagnosis, find themselves desperately seeking guidance from practitioners for resolution of systemic complaints. They may press medical care providers for a diagnosis which can result in treatment in the absence of definitive laboratory identified disease, an issue which has broad consequences. This situation, which results from the limitations of diagnostic testing and treatment options faced by providers and patients suffering from chronic illness, affects a large community of patients across the country including members of the military and their families. Furthermore, many have been quick to jump to the conclusion of a Lyme disease (LD) diagnosis due to a common perception of unreliable and inconsistent testing.[1,2] This development has provided the opportunity for LD to become the scapegoat of a variety of systemic and otherwise undiagnosed illnesses. Additionally, protocols differ between Infectious Diseases Society of America (IDSA) and the International Lyme and Associated Diseases Society (ILADS) guidelines and can lead to confusion in LD diagnoses.[3] For example, the IDSA, in alignment with the Center for Disease Control and Prevention (CDC), touts a clear decision-tree style, two-tier approach to the assessment and diagnosis of LD.[4] Alternatively, ILADS openly challenges the definitive aspects of the IDSA

approach and claims that its two-tier protocol does not adequately serve patients or providers.[5] Thus, it is critical to reiterate proper diagnoses really have an impact. It is the difference between initiating an appropriate intervention with positive improvement in symptom presentation or a patient whose condition inexplicably worsens to the point of disability.

During the medical review board process within the US Army, diagnoses can be rushed and based on empirical evidence in order to fit neatly into the diagnostic rating system utilized by the Army Physical Evaluation Board as well as Veterans Affairs. This process as well as the confusion between IDSA and ILADS protocols caused CLD to be focused on for this military patient, which led to years of various ineffective and damaging treatments. Ultimately, this patient ended up being empirically treated for clinically diagnosed CLD and lost his health and military career in the process.

Case Presentation

A 21-year-old male, Division I student-athlete patient presented with heart palpitations and frequent unprovoked adrenaline rushes and was sent to a health clinic in November 2015. Based on a normal cardiac exam, his symptoms were attributed to stress and no significant treatment was pursued. His condition continued to fluctuate in severity and symptomology, which led the treating physician to conduct the following serological testing and results in March 2016: Lyme disease—negative, thyroid peroxidase—negative, Epstein-Barr virus (EBV)—positive, and heterophile antibody test (monospot)—negative. At this point, the patient was diagnosed with EBV reactivation and prescribed rest and recovery. However, a few months later, in May 2016, he graduated and was commissioned but remained on medical hold since his symptoms had not subsided. At this time, he was prescribed further rest and recovery by another treating physician until symptoms resolved, at which point he could continue onto training. However, the patient never attended training since his persistent mononucleosis-like symptoms and history of traumatic brain injury from sports and military service caused concern for post-concussion syndrome.

The patient was seen by a team of health care providers who collaborated in assessing him with a final recommendation of rest and recovery. Hyperbaric oxygen therapy (HBOT) was also discussed, so the patient began HBOT therapy with a private physician. This therapy was discontinued after two sessions due to increasing symptoms (heart palpitations, flank pain, myalgia, neuropathy, etc). Searching for answers and now on active duty, in September 2016, the patient was seen by a new health care provider who requested follow on serological testing for LD. This test reported negative results, but the patient was clinically diagnosed with LD due to symptom presentation, potential for exposure in military training, and lack of other definitive findings.

The patient was subsequently treated with 30 days of doxycycline (150mg/day). Due to persistent neuro-immune symptoms after antibiotic treatment, the patient sought out a second opinion from a LD specialist. By December 2016, the specialist ordered multiple LD tests standard to the IDSA and the CDC requirements. All of the LD tests performed were negative, but another 30-day course of doxycycline (150mg/day) was prescribed. This treatment course led to worsening symptoms in much the same way as the HBOT did including joint pain, intermittent nerve pain, headaches, fatigue, cognitive difficulty, anxiety, mild depression, and increased chest and flank pain. These symptoms led the LD specialist in January 2017 to conclude that a Jarisch–Herxheimer reaction was occurring, so he had the patient submit a serum sample for further testing at an independent laboratory with non-traditional *Borrelia burgdorferi* (bacterial cause of Lyme disease) IGeneX testing.[6] The serological testing revealed the following results as defined by the lab: *Borrelia burgdorferi* IgG/M/A—low positive, *Babesiosis microti* IgG/M—low positive, and *Anaplasma phagocytophilum* (HGA) IgM—low positive. In response to these results, the LD specialist ordered another 30-day course of doxycycline at a larger dosage (300mg). However, the treatment was discontinued after 1 week because it caused increases in the patient's flank, nerve, and joint pain. Looking for further validation of the LD diagnosis, the LD specialist had the patient submit more follow up serological testing for *B. burgdorferi* via a different private laboratory, all producing negative results. The patient's symptoms persisted and continued to increase in severity including anxiety and depression, which prompted a recommendation to visit a physician practicing in functional medicine.

Upon review of the case and patient, this functional medicine physician initiated her own work-up focusing more on the potential of mycotoxicosis due to increased susceptibility with CLD and mold exposure within living and training environments. This included submitting a buccal sample for genetic testing[7] in April 2017, looking for genetic indications in general limitations in detoxification pathways. Results revealed a homozygous single nucleotide polymorphism (C677T: T/T) in the Methylenetetrahydrofolate Reductase (MTHFR) gene suggesting the patient may have low activity of the MTHFR enzyme, which is a key factor in metabolic detoxification.[8] Based on this result as well as the patient's

background history, the functional medicine specialist tested him in June 2017 with a mycotoxin urine panel, which revealed strong positive results for mycotoxicosis. This physician then made a diagnosis of mycotoxicosis in addition to the clinical LD diagnosis already received, and the patient started receiving weekly infusions of IV phosphatidylcholine (up to 10 amps), IV glutathione (1200 mg), and IV Leucovorin (10 mg), as well as subcutaneous methyl B12 (1000 ug) for the next 3 months.

The patient experienced minor improvements in fatigue and stamina before the treatment became too costly to sustain out-of-pocket and was terminated. Following shortly after treatment termination, in October 2017, the patient was retested by the functional medicine specialist with the mycotoxin urine panel yielding negative results. However, the patient was still symptomatic and worsening in other areas. At this same time, the patient was recommended to the Army Medical Review Board to determine medical fitness to continue serving as an active duty officer. Due to continued chronic fatigue-like symptoms into November 2017, the following tests were run by the functional medicine specialist as well as an Immunologist and Neurologist (both referred to the patient by the functional medicine specialist) up to January of 2018, while the patient continued to experience persistent symptoms: investigating abnormalities in C-reactive protein, Sjogren's antibody (Ab), hepatitis, anticardiolipin Ab, antineutrophil cytoplasmic Ab panel, antinuclear antibodies IFA, Lyme Ab, C6 *B. burgdorferi*, bartonella DNA PCR, West Nile virus PCR, TNF-alpha, sensory neuropathy Ab, vasoactive intestinal peptide, melanocyte stimulating hormone, total IgG and IgE, mannose binding lectin, tryptase, chromogranin, human leukocyte antigen B27, and C3a. All of these tests yielded negative results. However, abnormal elevations in inflammatory immune biomarkers, such as C4a were continually discovered during testing.

During this time, the patient was unable to perform moderate or strenuous physical exercise or cognitive activity due to the following symptoms: cognitive impairment affecting short-term memory and ability to focus, severe fatigue and post-exertion malaise, asthma and increasing allergic-type reactions with chemical and food sensitivities as well as histamine intolerance, and progression to heat/ultraviolet induced urticaria. Additionally, the patient struggled emotionally with anxiety, depression, environmental stimulation (such as bright and flashing lights and loud noises), and sensitivity to stress. As a result of all these tests, the patient was diagnosed with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) following resolved acute mycotoxicosis by the functional medicine specialist. However, ongoing investigation and findings continued in order to better understand the root cause of the CFS/ME. By February 2018, the Army Medical Evaluation Board found the patient unfit for military service, and he was subsequently medically retired in June 2018 receiving 100% Veterans Affairs disability rating for the following: "Lyme disease, mycotoxicosis, chronic fatigue syndrome, allergic rhinitis and vasomotor rhinitis (physical evaluation board (PEB) referred as chronic Lyme disease, mycotoxicosis and chronic fatigue syndrome)."

Discussion

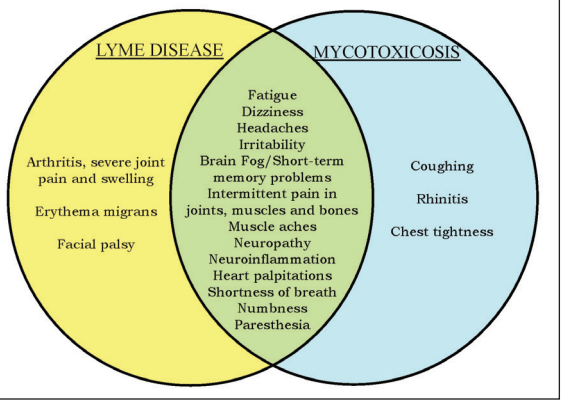
Here we present a set of complaints and diffuse symptoms commonly observed by medical practitioners. This presumptive case of CLD in the absence of clear and convincing laboratory confirmation and treatment guidelines, subsequent empiric therapy, and current practices by military medical boards resulted in the medical retirement of the service member. The current diagnosis and treatment of CLD is difficult at best for medical practitioners and may have serious unintended consequences for service members where military medical boards may make a presumptive determination of CLD and a recommendation for medical discharge in the absence of clear and convincing medical confirmation of disease.

This case shows how empirically treating and diagnosing symptoms can lead to a fishing expedition for the patient and multiple, unnecessary and potentially dangerous treatments. It also points to the importance of and need for clear testing/diagnosing guidelines. In this case, the numerous repeated seronegative results for *B. burgdorferi*, combined with the absence of erythema migrans and no known recent exposures, did not confirm a LD diagnosis. However, it is commonly accepted that LD, and, furthermore, CLD are clinically difficult to diagnose due to the sample type obtained for testing, the stage of the disease process, and the variations in the target type of the diagnostic assays used for detection.[1,2] Additionally, while both professional societies, IDSA and ILADS, continue to incorporate advances in laboratory-based diagnostic criteria or refinements in treatment regimes for LD, differences are pronounced, and patients are left with conflicting guidance. Furthermore, all of the currently available LD diagnostic tests have performance issues, which create concerns about the appropriate use and interpretation of these tests for both physicians and patients. So, when the low positive for *B. burgdorferi* on the non-traditional IGeneX test results were revealed, the LD diagnosis was believed to be solidified, especially when coupled with the presumed risk of the patient being exposed to *B. burgdorferi* infected

ticks because of his military duties.[9,10,11] These positive tests led to the preferred antimicrobial treatment for LD without any relief and, in fact, exacerbated the symptoms.

This worsening of symptoms prompted the subsequent testing of the patient for maladies to include mycotoxicosis. The patient had been exposed to mold in living and training locations, and there is a connection between CLD and increased susceptibility to other illnesses, including mycotoxicosis.[12,13] This susceptibility is thought to be because, although CLD patients may have antibodies to *B. burgdorferi* and generate memory B-cells to this pathogen, their humoral response is suppressed in the long term by the infection.[14] Additionally, although the symptoms of mycotoxicosis are dependent on the type of mycotoxin, length of exposure, age, sex, genetic predisposition, and prior health condition of the exposed individual, they include many of the same symptoms as CLD.[15] For this reason, it can be hard to distinguish between mycotoxicosis and LD when patients exhibit full-blown chronic symptoms of each (Figure 1).

Figure 1. Overlapping symptoms of Lyme disease and mycotoxicosis.



In regard to mycotoxicosis, the body's nonspecific immune defenses and detoxification pathways are typically able to eliminate mycotoxins as long as it is not suffering from some other chronic disorder or condition. In the case here, the patient had a MTHFR gene mutation. This specific mutation has been implicated in the MTHFR enzyme having a lower than normal activity with respect to methylation of protein intermediaries for a number of biochemical reactions in the body,[16] thereby potentially making exposure to mycotoxins much more difficult to control.

It is critical to highlight that while originating for different reasons, diagnoses such as CLD and mycotoxicosis share predominantly similar presentation of symptoms. This phenomenon is partly due to similar chronic activation of the immune complement system, in particular C3a and C4a, generating inflammation. In acute cases, spirochetes in LD and mycotoxins are both considered to be or to produce biotoxins, which perhaps leads to the shared symptomology. Complement proteins, C3a and C4a, are elevated in many LD patients. Symptomatic response to therapy in CLD often is associated with a decrease in C4a anaphylatoxins, whereas worsening symptoms often relates to an increase of this biomarker. Similarly, this inflammatory expression is seen following chronic mold exposure. Specifically, C3a levels will be normal while C4a levels will be elevated in mycotoxicosis.[17]

It is especially important to understand even the term chronic Lyme disease (CLD) can be confusing and refer to different patient populations that should not necessarily be grouped together. Four such populations include patients with post-treatment Lyme disease syndrome (PTLDS), patients with diffuse symptoms and unclear cause either diagnosed based on non-validated/unproven laboratory tests and/or clinical diagnosis, patients with an illness unrelated to *B. burgdorferi* infection, and patients exhibiting symptoms of late Lyme disease (encephalomyelitis, arthritis, etc.) who have antibodies against *B. burgdorferi*.[18] Of these four groups, most research and studies have been focused on PTLDS—how it is defined and possible causes.[19]

Ultimately, in the present case, it is unknown whether the military patient was initially exposed to *B. burgdorferi*, mycotoxins, or whether either of these two eventual diagnoses were actually responsible for initiating and progressing his illness. Yet, because of unreliable diagnostic testing and confusing standards for diagnosis, this patient was clinically diagnosed with LD and empirically treated for CLD and complications arising from it. This case serves as an example why it is extremely important to have clear guidelines surrounding a disease diagnosis and reliable, accurate diagnostic tests.

Conclusion

This case illustrates that an inappropriate clinical diagnosis and empirical treatment can be inherently detrimental to the health, safety, and well-being of the patient. Additionally, the amalgamation of perceived mistrust and limitations in LD testing combined with an eagerness to diagnose LD based on what may be considered "pseudoscience" is potentially harming patients with undiagnosed chronic illness. As far as the military's Medical Evaluation Board is concerned, a clinical diagnosis, whether confirmed with diagnostic tests or not, can result in removal of a service member from the military. This, along with the fact many chronic illnesses share

overlapping symptoms, beget the recommendation that resources be directed to further develop diagnostic tests and strategies to evaluate physical, neuro-cognitive, and behavioral symptoms alongside clinical testing in order to address the root cause of the illness. Potentially implementing genetic testing, immune complement (or other biomarker) testing, and imaging earlier in the diagnostic procedures of nonspecific and variable symptom presentation will lead to higher success rates in identifying predispositions, susceptibility, and co-infections as well as better inform effective and appropriate treatment. Ultimately, early detection and a more comprehensive understanding of and treatment plan for chronic conditions could help more service members return to being fit for duty, and restore the strength of our fighting force.

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Authors

LTC Vanessa R. Melanson is with the Chemistry and Life Sciences Department, United States Military Academy, West Point, NY.

CDT Kalei A. Hering is with Chemistry and Life Sciences Department, United States Military Academy, West Point, NY.

James L. Reilly is with Chemistry and Life Sciences Department, United States Military Academy, West Point, NY; John A. Feagin, Jr. Orthopaedic Sports Medicine Fellowship, Keller Army Community Hospital, West Point, NY; and The Geneva Foundation, Tacoma, WA.

1LT (ret) Joseph M. Frullaney is with Chemistry and Life Sciences Department, United States Military Academy, West Point, NY.

LTC (P) Jason C. Barnhill is with Chemistry and Life Sciences Department, United States Military Academy, West Point, NY.

The Paradox of Network Inequality: Differential Impacts of Status and Influence on Surgical Team Communication

LTC Christopher H. Stucky, PhD, RN, CNOR, CSSM, NEA-BC
COL (ret) Marla J. De Jong, PhD, RN, CCNS, FAAN
Felichism W. Kabo, PhD, M.Arch

Abstract

Introduction: Healthcare is a dynamic and complex system predisposed to adverse events caused by human and technical errors. The ability of multidisciplinary clinicians to effectively communicate clinical information influences healthcare quality. Authority gradients, culture, and organizational hierarchy frequently constrict communication and contribute to surgical adverse events. Hierarchy is especially pronounced in military medicine, where military status, rank, and professional roles potentially create barriers to communication.

Methods: We used an exploratory, prospective, cross-sectional design to determine how the social structure of military surgical teams influences group (network) communication effectiveness. Using a social network questionnaire, we surveyed members of surgical teams concerning their close-working relationships with other team members and perceptions of their communication effectiveness. We addressed the following research question: In surgical teams, how do the status (indegree) and influence (outdegree) of its individual members impact communication within the team?

Results: We surveyed 50 surgical teams comprised of 45 clinicians and found that for close-working relationship networks communication effectiveness improved with lower concentrations of status and higher concentrations of influence. Network indegree (i.e., status) (β=-0.893, p=.019) had a larger impact than outdegree (i.e., influence) (β=0.617, p=.015), indicating status had a larger effect on communication effectiveness than influence. Put simply, our results show communication improves when there is more equality of status in the surgical team. Paradoxically, communication improves when there are higher concentrations of network influence among surgical team members.

Conclusions: Inequality in surgical team networks has paradoxical effects on communication effectiveness. The impact of network structure on organizational behavior is of high interest to the military and provides essential insights into clinicians' ability to communicate in a highly complex and task-based environment. Communication will likely improve in surgical teams through methods to foster equality of team member status and promote surgical leadership. Military medical policies could both amplify the positive effects and mitigate the negative effects of network inequality.

Introduction

Healthcare is a dynamic and complex system predisposed to adverse events caused by human and technical errors.[1] Adverse events contribute to negative and catastrophic consequences for patients, including permanent injury and mortality.[2] Initiatives to ameliorate preventable harm are pervasive in the literature and often concern methods to improve technical skills,[3] refine policies and processes,[4] optimize workflows,[5] prevent medication errors,[6] and reduce infections.[7] However, errors attributable to nontechnical skills, such as communication, are a major contributor to adverse events.[8]

The ability of multidisciplinary clinicians to effectively communicate clinical information influences healthcare quality and safety. Authority gradients, culture, and organizational hierarchy frequently constrict communication and contribute to surgical adverse events.[9] Authority gradients and hierarchy are a particular concern for surgical teams, which are comprised of multidisciplinary clinicians with different levels of medical training, proficiency, and authority. Hierarchy is especially pronounced in military medicine, where military status,

rank, and professional roles potentially create barriers to communication.[10]

In *Keeping Patients Safe: Transforming the Work Environment of Nurses*, the Institute of Medicine determined hierarchy in health care organizations and poor communication are key contributors to medical errors.[11] Problems related to authority gradients and hierarchies cause disruptive behaviors, and the inability of all team members to speak up to improve processes and avoid safety issues.[12] Hierarchical gradients hinder communication and impede the flow and quality of collaboration between physicians and nurses.[9]

Surgery is characteristically structured in a hierarchical nature, as nurses and technologists routinely help surgeons perform tasks.[13] The surgeon, who provides direction to other team members, often dominates the task-based nature of surgical care[14] and the communication among team members.[15] Sevdalis and colleagues[15] studied intraoperative communication and found that during open surgeries surgeons initiated 81% (95% CI, 79-83) and received 46% (95% CI, 44-48) of all communication. This "Captain of the Ship"[16] approach potentially creates uneven patterns of communication and is not congruent with many current safety initiatives in healthcare, which contain measures to flatten hierarchies and limit dominance by any one profession.[17]

The social structure in the operating room (OR) is a system of interdependent social exchanges between clinicians and clinician groups who leverage each other for support or resources. Every healthcare team is comprised of members with varying degrees of status and influence, which accrue to an individual from one or a combination of skill, rank, knowledge, popularity, or authority. Typically, surgeons hold high-status on surgical teams.[13] High-status confers surgeons with communication advantages, as high-status team members have less difficulty speaking up in groups.[18] Additionally, being a focal or central recipient of communication provides surgeons with prestige and an enhanced ability to spread ideas and behaviors.[19] Furthermore, the ability to communicate easily provides certain team members with increased social influence.[19]

When conflict arises on surgical teams, it typically flows down the hierarchy.[20] This top-down direction of conflict can leave those residing on the lower end of the hierarchy not only feeling marginalized, but also bearing the brunt of the accumulation of conflict down the hierarchical structure. The consequence of hierarchy is that some groups and individuals possess a great ability to voice concerns and influence change, while others do not. Thus, the relationships among surgical team members influence their behavior, attitudes, and shape their communication practices. What is not clearly understood is how the social structure influences the ability of surgical team members to communicate effectively.

Statement of Purpose

The purpose of this study was to examine how the social structure of military surgical teams influences group (network) communication effectiveness. We addressed the following research question: In surgical teams, how do the status (indegree) and influence (outdegree) of its individual members impact communication within the team?

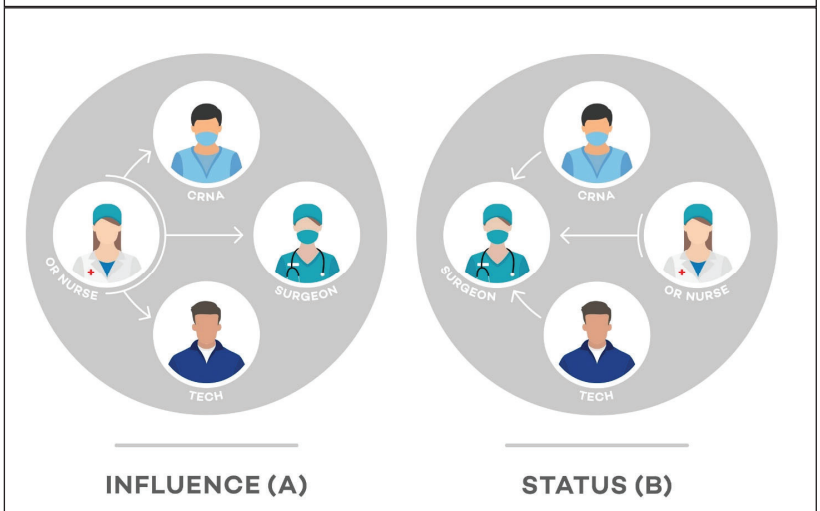
This research builds upon our previous investigations of surgical team communication. In previous papers, we examined the association between social distance (geodesic distance) and dyadic communication effectiveness[10] and characterized clinician communication patterns to provide insight into how interdependent clinician relationships influenced individual behavior.[21] In this manuscript, we provide novel insights into the social structure of military teams and examine the effects of status and influence on surgical team communication. Collectively, this body of work contributes to our efforts to identify operating room (OR) communication weaknesses, decrease healthcare induced risk, and promote safety.

Theoretical Framework

Social Network Analysis: In this study, we used social network analysis (SNA) as a theoretical and methodological approach to determine how the network social structure of relationships influence the overall ability of surgical teams to communicate effectively. SNA is a field of study based on the theoretical constructs of mathematics, psychology, sociology, and anthropology.[22] The impact of network structure on organizational behavior is of high interest to the military,[23] and researchers have applied network tenets to study many processes, including disease transmission, ecological networks, and gene expression.[19] The underlying assumption of SNA is the patterns of relationships influence behavior and actions.

Individual participants or groups comprise a social network and are connected by interpersonal relations referred to as ties. In social networks, the relational patterning of ties characterizes the social structure. The structure of network ties provides participants with opportunities or limitations, and their analysis can identify influential or isolated members or groups. The characteristics of social network structure determine the spread of information, diffusion of innovation, the cohesion of

Figure 1. Visual depiction of influence and status on surgical teams. Influence (A): The operating room (OR) nurse is an influential member with high outdegree and an ability to easily share knowledge with other network members. Status (B): The surgeon has high network status and high indegree because many others seek to direct ties to them.



**OR nurse = operating room/ perioperative nurse, CRNA = certified registered nurse anesthetist.*

membership, or sharing of resources.[22]

Researchers analyze social networks on the individual, dyadic or whole network levels.[22] Whole network analysis helps researchers understand connections among all participants in the network. In networks, the relational tie direction is either directed or undirected. Directed networks contain relations (ties) not necessarily mutual or reciprocated (e.g., seeks advice from), while undirected relational networks have no direction (e.g., works with). Directed networks have an indegree and outdegree measure. The summation of incoming ties represents indegree, while outdegree is the summation of outgoing ties. High indegree indicates network participant status and signifies popularity or prestige.[22] Participants with high indegree possess higher network status because many others seek to direct ties to them. High outdegree signifies network participant influence and signifies participant gregariousness with an ability to share knowledge.[22] Participants with high outdegree possess higher network influence because they can exchange and disperse information with others (Figure 1).[22]

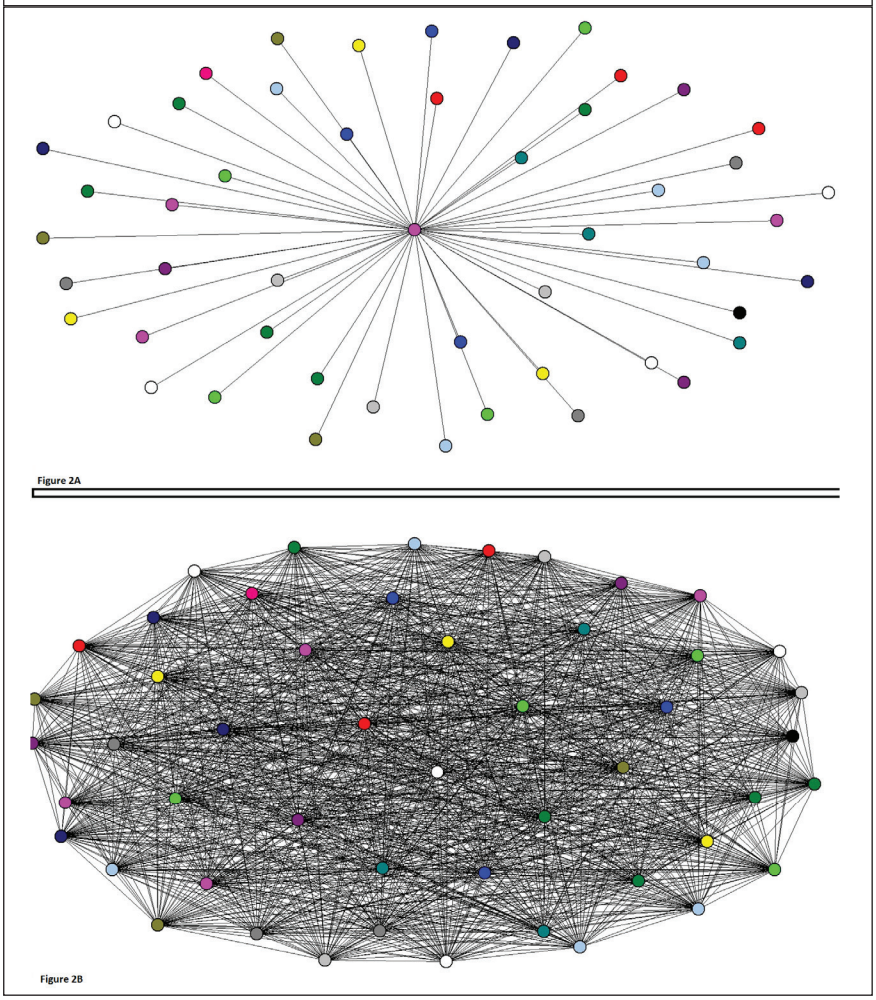
Network centralization depicts the distribution of power and influence within the network and indicates the degree to which a single participant dominates the social network.[22] Centralization ranges from 100%, where one participant is maximally central and all other participants are minimal, to 0% where there is an even dispersal of relationships and decision-making capabilities (or 0-1) (Figure 2). The extent to which information in the network flows from all other individuals to one participant describes high indegree centralization. One participant providing information to all other individuals in the network depicts high outdegree centralization. High concentrations of centralization indicate an unequal distribution of network positional advantage across the network. Thus, unequal levels of status (indegree) and influence (outdegree) are indicative of networks with inequality or variance in the flow of communication, information, and advice.

Methods

Design & Sample: We used an exploratory, prospective, cross-sectional design to determine how the social structure of military surgical teams influences group (network) communication effectiveness. This methodological approach is described in greater detail in Stucky et al.[10,21]

Participants: We conducted our study at a small Department of Defense (DOD) Air Force Military Treatment Facility (MTF) outpatient surgery center located in the southeastern US. We used total population sampling to recruit all interprofessional surgical team members who directly provide surgical care (active duty or civilian nurses, surgeons, anesthetists, and surgical technologists). The sample size estimation for SNA studies is dependent on the overall participation rate and network

Figure 2. Visual depiction of maximal and minimal centralization. 2A (Top): 100% centralization. This figure illustrates complete or maximal network centralization, where one participant is the focal participant (high indegree) because many others seek to direct ties to them. High indegree signifies a high-status member. 2B (Bottom): 0% centralization. This figure illustrates minimal network centralization where every participant has equal amounts of status and influence.



size. An 80% participation rate was targeted to generate robust results and limit biased inferences from missing data.[24]

Study Procedures: After the institutional review board approval, we recruited and enrolled participants. Participants voluntarily consented to participate in the study and provided demographic information. We expanded a network survey developed in previous studies by Kabo[25] and assessed its content validity through pilot tests in small groups. The principal investigator administered the anonymous survey spanning three months to surgical teams after the last daily surgical case. We chose the timing of the survey to mitigate disadvantages with retrospective data and minimize intrusion to the surgical workflow.

For a relational network, we chose to investigate the presence of a close-working relationship among the surgical clinicians. Teams with close-working relationships have shared experiences and confidence in the individual expertise of each member, which helps to form shared mental models.[26]

We asked participants to consider clinicians on their current surgical team and respond to survey items on close-working relationships (would you say that you have a close-working relationship with this person?), and communication effectiveness (How would you rate the quality of communication of each team member?). The participants answered (yes or no) for the close-working relationship item and rated others on their communication effectiveness from 1 (very low-quality communication)

to 5 (very good communication). Thus, the results from the survey informed the development of a close-working relationship network (range 0-1) and a communication effectiveness score for each individual (range 1-5). To analyze communication on the group level, we averaged and aggregated individual communication effectiveness scores per surgical team to develop a network communication effectiveness model.

Table 1. Summary statistics and correlations for communication effectiveness and centralization.

	Variable	Tie Direction	*Mean*	*SD*	Min	Max	1	2	3
1	Communication effectiveness	n/a	4.311	0.358	3.333	5	1.000		
2	*Indegree* Centralization (status)	Team to ego	0.276	0.146	0	0.750	-0.392*	1.000	
3	*Outdegree* Centralization (influence)	Ego to team	0.515	0.186	0	0.889	0.353*	-0.870	1.000

*$p < .05$ **$p < .01$ ***$p < .001$

Note: Communication effectiveness and centralization generated using "close working relationship" network

SD = standard deviation; Min = minimum; Max = maximum

Data Preparation & Analysis: SNA methodology requires arranging relational data into square matrices for analysis. We organized the data from the close-working relationship network and the communication effectiveness model into a full matrix format containing rows of participants and columns of attributes and adjacency matrices (rows and columns of participants connected by a tie).

We aggregated the individual communication effectiveness ratings to the team level for analysis and comparison. The aggregation of individual communication effectiveness ratings enabled us to identify teams with proficient or suboptimal communication. Since this study used directed networks (ties can be from a person to a person, or both from and to a person), outdegree and indegree measures depict network centralization. High indegree centralization indicates that other team members chose one focal person (aggregated team-reported) as having a close-working relationship. In contrast, high outdegree depicts one focal person (aggregated self-reported) selected a close-working relationship to all other surgical team members in the network.

For network data analysis, including the computation of centralization in the close-working relationship network, we used UCINET 6.625.[27] Additionally, we used STATA SE/14 to compute bivariate statistics and regression analyses.[28] Pearson product-moment correlation coefficients measured the strength of the linear association between centralization in the close-working relationship network and network communication effectiveness. We used multiple linear regression to determine how centralization in the close-working relationship network predicted whole network communication effectiveness. For regression, the communication effectiveness score was the group level dependent variable, and the predictor variables were outdegree and indegree centralization in the close-working relationship network. Due to the potential for high correlations between centralization scores across the outdegree and indegree networks, we assessed the variables using variance inflation factor tests (VIF) and found that multicollinearity was not a concern. To correct for within-subject correlation and increase precision, each model estimated clustered standard errors by team using the robust option in STATA. We set statistical significance at P<.05.

Results

We surveyed 50 surgical teams comprised of 45 multidisciplinary surgical clinicians, with many participants on multiple teams. In a previous paper, we described individual participant characteristics in more detail.[10,21] Briefly, the enrolled sample was predominately military, with 30 commissioned officers, 13 enlisted members, and four civilian employees. The sample comprised 13 surgical technologists, six perioperative nurses, 15 surgeons, two surgical residents, and 11 anesthetists who were predominately Caucasian, an average age of 35 years (standard deviation [SD]=9.1), and with six years (SD=4.6) of surgical clinical experience. We enrolled 47 clinicians, with 45 participants responding for a response rate of 96%.

Statistics and correlations for the network communication effectiveness model and network centralization are summarized in Table 1. The network communication effectiveness model (M=4.311, SD=0.358, [range 3.333-5]) showed considerable variation, indicating different levels of reported communication across the surgical teams. The close-working relationship indegree (M=0.276, SD=0.146, [range 0-0.750]) was 27.6% centralized, denoting a lower concentration of status and power. Conversely, the close-working relationship outdegree centralization (M=0.515, SD=0.186, [range 0-0.889]) network was 51.5% centralized, indicating higher concentrations of influence.

The analysis in Table 1 indicates network centralization can be both positively and negatively correlated with network communication effectiveness. There was a moderate and significant negative correlation between

communication effectiveness and indegree centralization (r=-0.392, p<.05), indicating that as concentrations in status decreases, communication effectiveness increases. In contrast, there was a moderate and significant positive correlation between communication effectiveness and outdegree centralization (r=-0.353, p<.05), indicating that as the concentration in influence increases, communication effectiveness increases.

Table 2. Regression results for communication effectiveness and network centralization.

Variables	Communication Effectiveness Model
Close-working Relationship Network	
Indegree Centralization	-0.893* (0.369)
Outdegree Centralization	0.617* (.246)
Constant	4.240*** (0.203)
Observations (number of unique longitudinal observations of 45 team members across 50 teams)	234
R-squared	0.256

Robust standard errors in parentheses
*** $p < .001$, ** $p < .01$, * $p < .05$

Table 2 contains the results for the multiple linear regression. The close-working relationship network indegree had a significant negative association (β=-0.893, p=.019) with network communication effectiveness, suggesting communication effectiveness worsened when one team member wielded too much status. The close-working relationship network outdegree had a significant positive association (β=0.617, p=.015) with network communication effectiveness, suggesting communication effectiveness improves when one central team member wields substantial influence. The indegree coefficient is larger than the outdegree coefficient, suggesting the status effect has a larger magnitude of impact on communication effectiveness than the influence effect.

Discussion

The main findings are in close-working relationship networks, communication effectiveness improved with lower concentrations of status and higher concentrations of influence. Network indegree (i.e., status) had a larger impact than outdegree (i.e., influence), indicating status had a larger effect on communication effectiveness than influence. Put simply, our results show communication improves when there is more equality of status in the surgical team, and higher levels of influence are also paradoxically beneficial to communication.

Surgeons, nurses, surgical technologists, and anesthesia providers with various backgrounds, roles, priorities, experiences, and clinical expertise comprise military surgical teams. The team ensures safe and quality care through a collective of interdependent tasks and activities. The effectiveness of military surgical teams and positive outcomes of surgery are influenced by communication (i.e., outdegree or influence), which also impacts other preventive measures, including situational awareness.

The ability of clinicians to voice critical information in the surgical environment is imperative to reduce risk and promote a safe culture.[29] Team members in lower status roles and professions sometimes avoid speaking up despite having something valuable to contribute. Communication will likely improve within surgical teams with even distributions of status, which also positively contributes to flattening hierarchies and authority gradients. Networks with lower concentrations of status facilitate sharing information from all team members and promote speaking up behaviors.[12] Thus, in networks with reduced levels of status and hierarchy, information sharing increases and a collective knowledge base forms, which is inclusive of all team members. Indeed, we found status had a larger effect on communication effectiveness than influence. This potentially indicates surgical team communication is influenced more by a reduction in status (created by rank, role, or responsibility) than by an influential member directing the team to accomplish tasks.

Mayo and colleagues[30] discuss the concept of smart teams in healthcare and challenge the belief that the smartest people comprise the best performing teams. Individual strengths and knowledge provide surgical teams with collective group intelligence. A high level of collective intelligence is essential in surgical teams, where many tasks are interdependent with a high degree of coordination. Collective intelligence assists the surgical team to coordinate activities, share information, complete patient care, solve problems, evolve, and thrive. Status and authority gradients can stifle collective intelligence.[30] Conversely, inclusive leadership—including valuing the unique contributions of all members—helps to flatten status, builds communicative relationships within the team, and increases team effectiveness.[31] Thus, flattening of status fosters knowledge sharing and enables the teams' collective knowledge to flourish.

The study highlights the importance of surgical leadership and how a focal person with higher influence to direct tasks and activities potentially benefits communication. Higher concentrations of influence led to better

levels of communication effectiveness. In stressful situations, this "Captain of the Ship" approach is important to delegate tasks and remove role uncertainty. Yet, surgical team leadership does not always have to rest in a single leader, as clinicians share many functions. However, Parker and colleagues[32] determined surgeons used more direct communication during times of unexpected occurrences, and the surgical team altered their behavior to meet the task changes. The researchers observed surgeons exhibiting leadership behaviors of guiding and supporting, communicating and coordinating, and managing tasks.[32] Although shared voice and promotion of a safety culture is essential, it is vital strong leaders direct communication when the task or situation necessitates.

The status and influence of surgical team members shape their communication practices and impact their ability to share ideas and influence change. However, high-status team members need not have the highest concentrations of influence. Members of the team with lower status may be well-positioned to broker honest communication among those with high network influence. Put simply, we recommend future research to answer the following question: Can we engineer network influence within surgical teams?

The exploration of network science in military-centric healthcare settings provides important knowledge about which factors promote the safety characteristics of mutual trust and effective communication. The results align with our previous findings,[10,21] which suggest that team cohesion is critical for improved communication and coordination of shared tasks and goals. Flattening uneven concentrations of status in military surgical teams may provide safety benefits and help form cohesive teams with superior military healthcare performance. Communication will likely improve in surgical teams through methods to foster equality of team member status and promote surgical leadership.

Limitations: The whole network level of analysis presents a limitation to this study, as the analysis does not isolate the individual contributions of participants. Thus, our findings do not discuss which individuals or groups of individuals dominate the network. Our previous findings discuss communication and relationships on the individual level and dyadic levels,[10,21] which provide further considerations for surgical service managers. Another limitation of this exploratory study is that we analyzed one type of network. Future research should investigate various types of networks, such as advice, interaction and socialization that influences surgical team communication. Lastly, the unique characteristics of this sample and setting—predominately military participants and a single Air Force MTF—potentially limit the generalizability of the findings to larger Military Health System components.

Conclusion

Our results show communication improves when there is more equality of status in the surgical team and when there are higher concentrations of network influence. The impact of network structure on organizational behavior is of high interest to the military,[23] and provides essential insights into clinicians' ability to communicate in a highly complex and task-based environment. The surgical setting is hierarchical by nature and comprises members with different levels of status and influence. Investigating the relational structure among military surgical team clinicians is vital to understand the safety culture and what inhibits or promotes effective communication. Communication will likely improve in surgical teams through methods to foster equality of team member status and promote surgical leadership. Military medical policies could both amplify the positive effects and mitigate the negative effects of network inequality.

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Authors

LTC Christopher H. Stucky is Nurse Scientist, Center for Nursing Science and Clinical Inquiry, Womack Army Medical Center, Fort Bragg, NC.

COL (ret) Marla J. De Jong is Dean, University of Utah College of Nursing, Salt Lake City, UT.

Felichism W. Kabo is Assistant Research Scientist, Survey Research Center, Institute for Social Research, University of Michigan, Ann Arbor, MI.

Lessons and Best Practices for Physical Therapy in Brigade Combat Team Operations

CPT Andrew B. Toman PT, DPT

Physical therapists (PT) have an integral role in supporting readiness of the Army warfighter. With an increased demand for active duty PTs and the transition to Defense Health Agency (DHA), more direct commission PTs and new graduates as first lieutenants will see themselves positioned in brigade combat teams (BCT). Traditionally, this role is given to a captain due to experience. Additionally, working in a forward deployed or rotational environment brings its own challenges encountered very seldom while in garrison. For example, military treatment facility (MTF) support for outlying clinics ensures continued ease of access to care for musculoskeletal conditions. Whereas in rotational environments, battalions are spread out across large geographic regions, thereby limiting continuity of care. As a brigade (BDE) PT, finding solutions is imperative to overcome these challenges, minimize the negative consequences of limited access, and find ways to address musculoskeletal (MSK) conditions requiring care.

Primary challenges of working in a BCT is there are a great number and diversity of units that function across larger areas.[1] Limited internet capabilities can negatively affect telehealth services. Courses of action to ensure regular physical therapy services can include a pre-established rotational schedule for the PT with their technician, typically a physical therapist specialist (68F). A secondary course of action includes the PT working closely with each battalion (BN) primary care manager (PCM) to plan travel on a demand basis. A careful balancing act must be performed to ensure access to care is not hindered in the PT primary footprint with the BCT.

Traveling on demand supports those areas that have the greatest need and reduces travel costs. A rotational schedule allows each BN to know ahead of time when PT services will be available; however, training schedules and field training exercises may cause frequent re-scheduling, negatively impacting patient care. Traveling on demand requires close communication with BN PCM to maintain situational awareness of patient demands and training schedules in order to plan travel via the Defense Travel System (DTS). As the BDE PT, it is in your best interest to communicate with your BN and BDE regarding the DTS standard operating procedure (SOP) in order to travel with commercial airlines. DTS processes can commonly require funding memos, concept of operations, and BN commander support requesting you specifically through BDE commander and BDE surgeon. Traveling in groups with other specialty providers is a way to reduce costs and improve efficiency of travel by transportation motor pool or rental car. Planning travel from one BN area to another will reduce meal and lodging expenses if performing multi-site visits. If travel opportunities are limited or restricted based on mission demand or BDE level restrictions for travel, telehealth may be the best option for improving patient access to care.

Telehealth is a service commonly provided by behavioral health officers in rotational environments, and has been gaining momentum with physical therapy services in civilian rural communities. Contingent on reliable network connectivity, physical therapy evaluations can be conducted in a Health Insurance Portability and Accountability Act (HIPAA) compliant room with video capabilities. For an effective physical therapy telehealth evaluation it is important to have a trained presenter. This presenter ideally is a medic who is trained in the fundamentals of range of motion, strength testing, special tests, and patient positioning. Combat medic (68W) training is challenging while on rotation, and as such should be completed prior to departing permanent duty station.

Cross training combat medics to implement basic home exercise programs can serve as a method of providing early access to care for acute and acute on chronic conditions in rotational environments. Mirroring the example in MTF rehabilitation departments that implement group classes for the upper extremity, lower extremity, and core/low back from the BDE PT can adjust based on equipment available. Implementation of the courses while on rotation depends on each BN and establishing an SOP with the PCM and trained medics for time and location. Classes should be provided for a finite number of visits in order to equip the soldier-patient with proper technique for a home exercise program, determine that

formalized physical therapy evaluation is warranted, or referral for advanced imaging. Further training for medics at BN levels should include appropriate musculoskeletal screening for appropriateness to physical therapy classes. Supporting resources include military injury control screening found in Training Circulate 8-280, and Soldier Training Publication (STP) 8-68F13-SM-TG.[2,3] If staffed with a physical therapy specialist, he or she can serve as an additional resource for training combat medics.

Building relationships with referring providers throughout rotations and time spent in a BCT is crucial for optimal patient outcomes. Clear lines of communication and expectations can help ensure that upon arrival to outlying areas the PT is already equipped with appropriate Class VIII supplies. Frequent communication with PCMs can help the physical therapist coordinate schedules with other BNs and be equipped to plan ahead for future travel throughout the BDE footprint. Having a strong relationship with referring providers helps ensure patient profiling is in accordance with evidence-based practices and minimizes deleterious effects on mission capabilities.

Physical therapists play a crucial role in soldier readiness, and ensuring access to PT services supports this mission. Planning ahead and coordinating access to care throughout large geographic and international lines is an integral part of rotational assignments. Training medics and ensuring the physical therapy specialist is credentialed and qualified is no easy task. As a MSK subject matter expert, it is up to the PT to build a toolbox and set the example. Prior to rotation, obtain additional training beyond what entry level PT programs trained you to do. Consider obtaining a certification in trigger point dry needling, improving osteopathic manipulative techniques, and continued education courses on telehealth to improve and refine your toolbox. Lastly, continue to network with other PTs who have been on similar rotations to learn from their experiences and apply to your own.

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Author

CPT Andrew B. Toman is Board Certified Clinical Specialist in Orthopaedics, Certified Strength and Conditioning Specialist, and 1 CD 2 ABCT Brigade Physical Therapist.

Demonstration and Evaluation of Physical Examination Techniques Intended to Identify Proximal Femoral Bone Stress Injuries

Mark Thelen, PT, DSc
Thomas Sutlive, PT, PhD
LTC Bradley Tragord, PT, DSc
LTC David Robbins, PT, PhD
1LT Ryan Schiferl, SPT
1LT Breanna Brock, SPT
1LT Krystin Demsher, SPT
1LT Ashlynn Godin, SPT
1LT Kyle Anstead, SPT

Abstract

Purpose: Proximal femoral bone stress injuries (BSI), especially those involving the femoral neck (FNBSI), pose a risk to military medical readiness. There is currently no optimal physical examination technique or test item cluster that substantially influences the clinical diagnosis of FNBSI. Consequently, a lower threshold to order diagnostic imaging is employed by clinicians who manage military populations at risk for FNBSI. A viable physical examination technique or cluster of techniques is needed to better inform this clinical decision process and reduce the associated diagnostic imaging burden. This project assessed the perceived clinical utility of several novel physical examination techniques intended to identify proximal femoral bone stress injuries.

Methods: Thirteen FNBSI-specific physical examination techniques were evaluated using standardized grading criteria, evaluating safety, reliability, and credibility. Based on group consensus, two weight-bearing techniques—forward lunge and tap (FLT), rear lunge reach and tap (RLRT)—and three non-weight-bearing techniques—proximal femoral shear test, 45-degree compress and percuss, and the side-lying scissor test—were each determined to possess a parsimonious cluster of desirable examination properties. A one-hour, multimedia presentation accompanied by live demonstrations was presented to 13 clinicians. Each clinician rated the physical examination techniques based on the following five criteria: patient safety, likely to identify only bone pathology, accuracy regardless of symptom duration or acuity, performed in the mid-range of available motion, and reliability. These criteria were individually weighted from 1 (strongly disagree) to 5 (strongly agree), yielding a possible maximum score of 25. Each physical examination technique was also given a yes or no rating for overall credibility. The minimum acceptable value was set *a priori* at 80% yes votes.

Results: All clinicians in attendance were physical therapists with an average of 5.9 (SD: 4.4) years of experience managing patients with FNBSI. All attendees either agreed or strongly agreed all techniques would be safe to use with patients suspected of having a FNBSI. The highest overall scoring test based on the five criteria was the FLT with a score of 21. The only two tests to exceed the 80% benchmark for overall credibility were the FLT (92.3%) and the RLRT (83.3%). There were no overall statistically significant differences within each individual criterion except for the safety criterion. However, post hoc pairwise comparisons revealed no statistically significant differences.

Conclusions: A minimum of two of the novel physical examination techniques (FLT, RLRT) appear to have sufficient credibility to warrant further evaluation based on voting results from an experienced group of clinicians. A concurrent criterion validity study to assess the diagnostic accuracy properties associated with these techniques is now indicated.

Clinical Relevance: This line of research may assist future clinicians to determine the need for diagnostic imaging procedures in patients with a suspected FNBSI.

Introduction

Femoral neck bone stress injuries (FNBSI) represent both diagnostic and management concerns for the US military healthcare system.[1,2] They are considered a high risk bone stress injury due to increased risk of non-union, delayed union, and progression to complete fracture. While bone stress injuries (BSI) are relatively common in the US military, especially within initial entry training programs, FNBSI are relatively uncommon. From 2003-2012, FNBSI accounted for less than 0.04% of all stress fractures reported for active component members of the US Armed Forces.[3] FNBSI are identified reliably with appropriate diagnostic imaging studies; however, the gold standard of magnetic resonance imaging (MRI) is an expensive and limited resource. Furthermore, there is no consensus regarding the optimal clinical pathway to trigger the decision to request such studies. Consequently, clinicians who support military populations are prone to employ a lower threshold for ordering confirmatory imaging studies.[4,5]

Clinical suspicion for BSI stemming from the objective examination is frequently based on localized tenderness to palpation. However, direct palpation at the proximal femur is not possible, forcing clinicians to rely on other physical examination techniques. To date, there have been no high-quality diagnostic accuracy studies to suggest any physical examination technique will significantly shift the post-test probability for or against the presence of a FNBSI. Previously reported physical examination techniques that may help identify this type of injury include the following: Fist Test,[6] Patellar Pubic Percussion Test (PPPT),[7,8] Barford Test,[9] heel percussion test,[10] log roll,[11] and hopping on the symptomatic lower extremity.[12] It may also be useful to review biomechanical studies that analyze different functional movements and their ability to provoke stress at the proximal femoral neck. For example, Qian et al[13] reported during the forward lunge and backward lunge greater mechanical stress was observed on both the compression and tension sides of the femoral neck as compared to other basic functional movements.

The Fist Test was introduced as a part of an overall lower extremity stress fracture assessment protocol.[6] The authors reported the overall incidence of femoral stress fractures in military trainees, but did not specify the anatomic locations of the injuries, which were identified by bone scintigraphy. Further, the test uses the examiners body weight transmitted only to the anterior thighs through the fists while the patient is in a seated position. Therefore, it is unknown to what extent the reported sensitivity of 74% and specificity of 89% would apply for detecting FNBSI.

The PPPT reportedly has excellent diagnostic accuracy when used to detect the presence of an occult hip fracture associated with trauma. It has a pooled sensitivity of 95% and specificity of 86%.[7,8] However, no diagnostic accuracy study has examined the use of the PPPT in a young, active population clinically suspected of having a FNBSI. Further, it may not be reasonable to expect this test to be sensitive enough to detect sound conduction differences in FNBSI, especially with lower grades of injury.

Therapeutic ultrasound has a pooled sensitivity of 64% and specificity of 63% when detecting lower extremity stress fractures.[14] No study has examined the use of therapeutic ultrasound to detect FNBSI. Given the anatomic depth of the femoral neck, it may not be reasonable to assume the stimulus provided by therapeutic ultrasound would be sufficient to provoke symptoms in a patient with a suspected BSI in this region.

Tuning forks have also been studied regarding the accuracy with which symptoms can be provoked when applied to the suspected site of a BSI. Tuning forks are commonly available in three different frequencies: 128 Hz, 256 Hz, and 512 Hz. As compared to radiographs, MRI, and bone scan, sensitivity when using the 256 Hz tuning fork was the highest at 92.3%, 90.0%, and 77.7%, respectively.[14] Jawad et al[15] used a tuning fork (128 Hz) and an electronic stethoscope to measure sound conduction through bone and reported a sensitivity of 78%, specificity of 82%, and positive likelihood ratio of 4.3, but the sample consisted of subjects aged 79-85 years old with post-traumatic hip pain and normal radiographs. The Barford Test also reported higher sensitivity (91%)[9] but has not been shown to be applicable to patients with femoral neck bone stress injuries (FNBSI).

The heel percussion test is commonly used in clinical practice, but to our knowledge, no study has formally reported its diagnostic accuracy. Based on a retrospective cohort of 54 patients diagnosed with a FNBSI, Fullerton and Snowdy[10] reported only 5.6% had a positive heel percussion test. Additionally, no study to date has examined the diagnostic accuracy for the log roll or for a hop test. However, in a cohort of 71 athletes with femoral BSIs, 70.3% had pain reproduction when hopping on the injured side.[12]

Without reliable and valid physical examination techniques, a lower threshold for ordering musculoskeletal imaging studies to promptly diagnose and properly manage patients with a suspected FNBSI is currently necessary. In two large retrospective cohorts involving active duty military patients clinically suspected of having FNBSI, only 171 out of 881 (19.4%) were confirmed

by MRI.[16,17] Based on this collective estimate, military clinicians may willingly take on an approximately 80% false positive rate when relying on clinical examination to diagnose FNBSI correctly. Practice recommendations, such as those published by Dembowski et al,[4] also suggest minimal symptomology to achieve clinical concern for a hip BSI. They suggest a patient with any risk factors for BSI and complaints of pain in the hip, pelvis, or buttock region should promptly receive radiographs and possibly MRI examinations. While these recommendations are reasonable and well supported in the literature,[5] they may, in part, contribute to the burden.

Table 1. Physical examination technique grading criteria.

CRITERIA	DESCRIPTION
Safety*	The physical examination technique would not cause an injury during the evaluation
Likely Bone-Specific*	The physical examination technique would provoke symptoms if bone pathology was present
All Levels of Acuity*	The physical examination technique would detect BSI regardless of the time since injury or the stage of the injury
Mid-Range*	The physical examination technique did not involve end ranges of movement
Reliability*	The physical examination technique can yield consistent results with multiple clinicians performing it on the same patient
Overall credibility#	The physical examination technique was considered credible (rating of perceived clinical utility / face validity)

** Criteria were weighed on an ordinal scale of (1-5), with 1=Strongly Disagree, 2=Disagree, 3=Neither Agree Nor Disagree, 4=Agree, and 5=Strongly Agree. # Dichotomous Yes/No rating.*

FNBSIs have classically been reported as compression sided injuries, tension sided injuries, or displaced fractures.[10] In the military population there is a definitively higher reporting rate of compression sided FNBSI. Based on our review of the literature involving US military personnel with FNBSI where the anatomic location of injury was also reported, an overwhelming majority occurred on the compression side.[10,11,16-19]

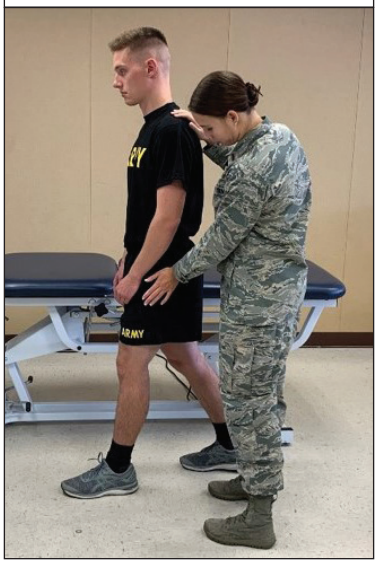
FNBSI can also be further classified based on the location from proximal to distal along the femoral neck, and the basicervical region of the compression side has been frequently identified as the site of FNBSI.[16] This region is located at the junction of the base of the femoral neck and the intertrochanteric region. It has been theorized that a majority of FNBSI specifically begin at the lesser trochanter primarily due to chronic traction forces resulting from repetitive iliopsoas muscle activity.[16,20] Additionally, Yang et al[21] reported simulated iliopsoas contractions could produce femoral neck fractures in elderly cadaveric femurs. Therefore, it is plausible muscle contraction may be a useful component of a physical examination technique intending to provoke symptoms within this region.

The development of any novel physical examination techniques intended to identify FNBSI should consider several factors to include the following: reported methods effective for identifying BSI in other anatomic locations, as well as proposed biomechanical theories regarding the distribution of stress across the proximal femur. Additionally, they should seek to safely and consistently provide a stimulus likely to provoke symptoms specifically within the proximal femur, ideally at the femoral neck. The purpose of this study was to assess the perceived clinical utility of several novel physical examination techniques intended to identify proximal femoral bone stress injuries.

Methods

Five novel physical examination techniques were selected from an initial 13 proposed examination techniques based on group consensus using grading criteria (Table 1). The five techniques were introduced to a volunteer audience of 13 clinicians using a one-hour multi-media presentation accompanied by live demonstrations which occurred during June 2020. A brief question and answer period followed at the conclusion of each demonstration. Attendees were given an opportunity to anonymously complete a brief questionnaire that requested descriptive information regarding their clinical background and experience treating BSIs. A survey was also completed which allowed for the qualitative grading of each of the five physical examination techniques, again using grading criteria (Table 1).

Figure 1. Forward lunge and tap.



The physical examination techniques were presented in a random order starting with the forward lunge and tap (FLT) (Figure 1). The steps for performing this technique were as follows: the patient was asked to perform a partial forward lunge with the affected leg (until the trailing heel came off the ground, signifying weight had been transferred to the affected lower extremity). The examiner stood posterolaterally relative to the affected limb while providing contact guard to the ipsilateral shoulder and then gently tapped the most superficial

Figure 2. Rear lunge reach and tap (RLRT).

Figure 3. Proximal femoral shear test (PFST).

aspect of the greater trochanter three times using the thenar eminence. The amount of force provided by the examiner when tapping the greater trochanter was consistent with the level of force applied when eliciting a patellar tendon reflex using a reflex hammer. A positive test would be signified by the reproduction or exacerbation of familiar symptoms in the hip region.

The rear lunge, reach, and tap (RLRT) (Figure 2) was the second physical examination technique presented. The steps for performing this technique were as follows: the patient stood in a symmetric but narrow, bilateral stance, and placed the toes of the affected lower extremity in line with the heel of the unaffected lower extremity. The patient then actively extended the knee of the affected lower extremity to produce hip extension (Figure 2A). Next, the patient then reached away from the affected lower extremity by sliding the hand on the unaffected side down the back of the thigh on the unaffected lower extremity (Figure 2B). The examiner was positioned posterolaterally to the patient's affected side with contact guard on the patient's ipsilateral shoulder. Next, the examiner gently tapped three times at the most superficial aspect of the greater trochanter on the affected lower extremity using the thenar eminence and using the same level of force described for the FLT. A positive test would be signified by the reproduction or exacerbation of familiar symptoms in the hip region.

The proximal femoral shear test (PFST) was the third physical examination technique presented (Figure 3). The steps to perform this technique are as follows: the patient laid supine in a partial hook-lying position. The examiner was positioned on the affected side, facing and centered on lateral aspect of the patient's knee. The examiner placed the heel of the superior hand on the proximal anterior thigh and the inferior hand at the proximal anterior tibia. The examiner then gradually applied a progressive load with an inferiorly and posteriorly directed force for no more than three seconds through the superior hand against the stabilizing inferior hand. Pressure would be released immediately if symptoms were provoked prior to three seconds. A positive test would be signified by the reproduction or exacerbation of familiar symptoms in the hip region.

The 45-degree compress and percuss was the fourth physical examination technique presented (Figure 4). The steps for this technique are as follows: the model patient laid supine in partial hook-lying with the affected hip and knee at approximately 45 degrees and 90 degrees of flexion respectively. With the examiner standing on the affected side of the model patient while facing the patient's head, and using both hands placed on the inferior aspect of the femoral condyles, a superiorly-directed force was applied in line with the shaft of femur to first resistance (signified by initial superior translation of

Figure 4. Forty-five degree compress and percuss.

Figure 5. Side-lying scissor test (SST).

the hemi-pelvis). This position was held using the outside hand. Next, the examiner percussed the inferior aspect of the medial femoral condyle three times with the blunt end of a triangle-shaped reflex hammer using the inside hand. Alternatively, it would be acceptable to use a vibrating 256-Hz tuning fork for 5 seconds applied to the medial femoral condyle. This would be appropriate in a case where patient sensitivity in the knee region would preclude the application of percussion. A positive test would be signified by reproduction or exacerbation of familiar symptoms in the hip region.

The side-lying scissor test (SST) was the final physical examination technique presented (Figure 5). The steps for this technique are as follows: the patient was side-lying with the affected lower extremity facing up and then placed behind the unaffected lower extremity (resting in slight hip adduction and extension). The examiner, standing behind the patient and stabilizing the superior hip, placed their arm between lower extremities at the level of the distal thigh and asked the patient to contract hip flexors isometrically against the examiner's stationary arm. A positive test would be signified by reproduction or exacerbation of familiar symptoms in the hip region.

All statistical analyses were completed using standard commercial statistical software. Descriptive statistics regarding clinical demographics were compiled from the volunteer group of presentation attendees and reported as means and standard deviations. A total of six qualitative criteria were measured for each physical examination technique. Five were measured on a five point ordinal scale, and one was measured dichotomously. Individual ordinal criterion scores were summed to produce a total quality score ranging from 5 to 25. Median and range of individual criterion and total quality scores for each physical examination technique were reported and ranked. The overall credibility score was measured dichotomously and reported by frequency counts and percentages of yes or no votes. If an attendee gave a yes vote for overall credibility to more than one technique, they were instructed to place the techniques in order of preference. The *a priori* overall credibility score that denoted an acceptable level of face validity was set at 80% yes votes.[22] A Friedman Analysis of Variance of Ranks was run to assess for any statistically significant differences within each individual criterion. Dunn's post hoc pairwise comparisons were performed as indicated. The protocol for this project was reviewed and given a non-research determination; therefore, no Institutional Review Board oversight was required.

Table 2. Clinical characteristics of attendees (n=13).

	Mean ± SD	Min	Max
Clinical Experience (years)	7.75 ± 4.81	0.75	19
Experience Managing BSI (years)	5.92 ± 4.83	0	15

Results

All 13 volunteer attendees were licensed physical therapists. Eight possessed at least one clinical specialist certification (61.5%), and most had clinical experience managing BSIs (Table 2). Qualitative criteria scoring for each physical examination technique are reported by median and range (Table 3). All attendees either agreed or strongly agreed the five physical examination techniques would be safe to employ with patients suspected of having a FN-BSI. This was considered the most important

Table 3. Qualitative criteria scoring for physical examination techniques.

	Safety	Likely Bone-Specific	All Levels of	Mid-Range	Reliable	Total Score
Forward Lunge & Tap	5 (4,5)	3 (2,3)	4 (1,5)	4 (3,5)	4 (2,5)	21 (16,23)
45-Degree Compress & Percuss	5 (4,5)	4 (3,5)	3 (1,5)	4 (3,5)	4 (2,5)	20 (15, 24)
Side-lying Scissor Test	5 (4,5)	3 (2,5)	3 (1,5)	4 (3,5)	4 (2, 5)	19 (16, 24)
Rear Lunge Reach & Tap	5 (4,5)	3 (2,5)	4 (1,5)	4 (3,5)	4 (2,5)	19 (16,22)
Proximal Femoral Shear Test	5 (4,5)	4 (2,5)	3 (1,5)	4 (3,5)	3 (2,5)	18 (16, 24)

- *Scores presented as median (range)*

individual criterion *a priori*. The techniques also scored similarly for central tendency regarding reliability and detecting BSI with mid-range positioning. However, more variability was observed when considering patients who present with different symptom severity and/or duration, as well as being able to preferentially detect an injury to the bone. The highest scoring technique was the FLT with a median (range) of 21 (16, 23). There were no statistically significant differences within each individual criterion except for the safety criterion, where an overall difference was observed ($\chi r2(4)=12.0$, $p=0.017$). However, subsequent post hoc comparisons with or without Bonferroni correction failed to reveal any statistically significant pairwise differences between techniques. The mean safety raw score (mean rank) were 4.54 (2.54) for the FLT and RLRT and 4.85 (3.31) for all other techniques. Table 4 outlines the order of preference reported by attendees for any techniques given an overall credibility vote of yes. The most common first choice selection was the FLT (53%), and the most common second choice selection was the RLRT (54.5%). The proportion of overall credibility votes ranged from 33.3% to 92.3% (Table 5), and only two techniques exceeded the *a priori* standard of 80% credibility: the FLT (92.3%) and the RLRT (83.3%). Although 13 attendees were present, all but one of the techniques received 12 votes due to one attendee only placing a credibility vote for the FLT.

Table 4. Order of preference summary.

	1ST CHOICE	2ND CHOICE	3RD CHOICE
Forward Lunge & Tap	7 (53.8%)	1 (9.1%)	1 (20%)
Proximal Femoral Shear Test	2 (16.7%)	1 (9.1%)	1 (20%)
Rear Lunge Reach & Tap	1 (8.3%)	6 (54.5%)	1 (20%)
45-Degree Compress & Percuss	1 (8.3%)	2 (18.2%)	2 (40%)
Side-lying Scissor Test	1 (8.3%)	1 (9.1%)	1 (20%)

Discussion

Based on the qualitative criteria established for this project, the FLT and RLRT had the greatest perceived clinical utility. However, further research is necessary to determine the actual safety and diagnostic accuracy of these techniques when employed in a clinical setting. There was no intent to generalize the results of this project into clinical practice. Rather, it was the first step in a deliberate process to identify if any novel physical examination techniques would be deemed credible enough to subject them to additional scientific inquiry.

Face validity was measured in this project using a unique qualitative survey. In a study targeting practicing clinicians and inter-professional collaboration, survey responses from professionals in the relevant field were also used to establish face validity and narrow down their field of interest for a training session.[23] Face validity may also be used to provide justification for additional studies. In the development of surgical training techniques, face validity has been utilized as a method of systematically receiving expert feedback in the early development stages and helped refine clinical application and implementation.[24,25]

This project's primary limitation is that these techniques were presented to a small, homogeneous group of clinicians consisting only of physical therapists who encounter FNBSI. It is possible that a larger group representing additional clinical specialties could have provided different overall results. Given the environmental constraints due to the COVID-19 pandemic, another limitation is that the attendees simply observed the techniques being performed by the presenters and were unable to physically practice them on a partner. The attendees were unable to gain an understanding of the tactile feedback of each test, which may have limited them in their understanding of the forces provided. The original intent was to identify physical examination techniques capable of specifically identifying FNBSI, given the burden associated with that type of BSI. Additional consideration yielded a collective opinion that these indirect techniques could also affect regions of the femur slightly proximal and distal to the neck. For the purpose of this project, the proximal femur was operationally defined as the region proximal to and including the lesser trochanter. Therefore, it is a known possibility that these techniques may not be useful for identifying FNBSI exclusively.

Table 5. Overall credibility vote summary.

TEST	YES	NO	PERCENT
Forward Lunge & Tap	12	1	92.3
Rear Lunge Reach & Tap	10	2	83.3
Proximal Femoral Shear Test	7	5	58.3
45-Degree Compress & Percuss	7	5	58.3
Side-lying Scissor Test	4	8	33.3

Conclusion

The highest scoring and most credible technique was the FLT, while the only other technique that met the overall credibility benchmark of 80% was the RLRT. Overall, these

results will assist in planning future research to determine the clinical utility of these techniques. Specifically, a diagnostic accuracy study comparing the FLT and RLRT against an appropriate criterion, such as magnetic resonance imaging (MRI), is warranted.

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Authors

All authors are with Army-Baylor University Doctoral Program in Physical Therapy, Fort Sam Houston JBSA, TX

Neodymium-Doped Yttrium Aluminum Garnet Laser Photobiomodulation May Improve Neurosensory Function after Surgical Injury to Cranial Nerve V: A Report of Three Consecutive Cases

CPT Sarah M. Vargas
CPT Megan E. Bunting
CPT Richard B. Hill
CPT Rachel J. Duval
COL Douglas D. Lancaster
COL Thomas M. Johnson

Abstract

Objective: The purpose of this report was to document clinical responses to Nd:YAG laser energy in patients with surgical injury to terminal branches of the trigeminal nerve.

Background: Limited evidence from in vitro, animal, and human studies suggests infrared laser energy may positively influence recovery after peripheral or cranial nerve injury, although clinical effects of neodymium-doped yttrium aluminum garnet (Nd:YAG) lasers remain unstudied in this context.

Methods: We applied Nd:YAG laser energy in the treatment of three consecutive patients presenting with altered neurosensory function following various oral and maxillofacial procedures. The time interval between surgical injury and laser photobiomodulation ranged from one week to two years.

Results: All patients exhibited reduction in the area of diminished sensation and partial recovery of normal neurosensory function. The two patients with long-standing neurosensory deficiency experienced near complete recovery of intraoral sensation, with residual zones of diminished sensation from the perioral skin.

Conclusions: Although all patients in this case series demonstrated clinical improvements compared with baseline, controlled studies are needed to determine whether Nd:YAG laser energy accelerates or enhances recovery of neurosensory function after surgical nerve injury. Studies establishing the relative efficacies of Nd:YAG and diode lasers appear warranted.

Keywords: lasers, paresthesia, electrophysiology, nerve regeneration, sensation, treatment outcome

Introduction

Injury to peripheral and cranial nerves resulting from trauma or surgery occurs commonly, and such impairments can substantially decrease quality of life.[1,2] Nerves sustaining minor damage often regain normal function without intervention, and in more severe injuries, surgical repair may offer functional sensory recovery.[3] However, there are limits to the innate regenerative potential of nerve tissue.[4]

Broad injury classifications, based on the degree of nerve discontinuity, include neurapraxia, axonotmesis, and neurotmesis. Neurapraxia involves loss of function without interruption of the structural integrity of the nerve.[5] This condition is usually transient and may result from postsurgical swelling applying pressure against a nerve. In axonotmesis, the perineurium and epineurium are preserved; however, the axon and surrounding myelin exhibit complete interruption.[5] Neurotmesis, the most severe type of nerve injury, involves partial or complete

nerve transection, and recovery may be unlikely without surgical intervention.[5] Neurorrhaphy, however, is often considered unacceptably invasive, except in the setting of complete nerve transection with attendant severe loss of neurosensory function.[6] Thus, pharmacological treatment and noninvasive adjuncts remain important in the management of many surgical nerve injuries.[6]

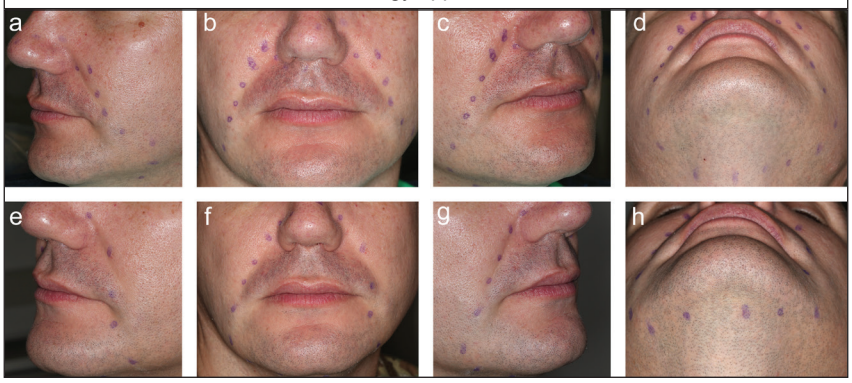


Figure 1. Baseline neurosensory deficit mapping (a through f) and progress following four laser biostimulation treatments (e through h). The follow-up mapping occurred three months after the initial laser energy application.

One approach for enhancing nerve regeneration and functional sensory recovery involves the use of various infrared lasers for photobiomodulation (PBM). According to the World Association of Laser Therapy (WALT), PBM—also called low-level laser therapy or biostimulation—occurs when light induces nonthermal photophysical and photochemical events in target cells or tissues, leading to physiological changes at various biologic scales.[7] Typical fluence (energy density) and irradiance (power density) applied in PBM are 1 to 20 J/cm^2 and 5 to 50 mW/cm^2, respectively, although much higher values are possible, depending upon the spot size.[8] Laser treatment at high power and energy values (high-level laser therapy) generates photothermal tissue effects, with adjacent zones exhibiting PBM as light penetrates and scatters into surrounding tissue.[9]

As early as the 1970s, investigators realized red and near infrared (NIR) light may enhance regeneration of traumatized nerves.[10] In multiple experiments using a rat sciatic nerve injury model, low energy continuous wave (CW) helium-neon (HeNe, 632.8 nm) laser irradiation produced a sustained electrophysiological effect, increasing nerve action potential eight months following laser energy application.[11,12] Contrary to these findings, a double-blind, controlled human study utilizing HeNe laser irradiation at 1 mW found no differences in action potential amplitudes, distal latencies, or skin temperatures between treated and control groups.[13]

In addition to HeNe lasers, investigators have also studied the ability of NIR diode lasers to stimulate nerve regeneration. In a rat median nerve injury model, CW indium gallium (aluminum) arsenide (InGa(Al)As, 808 nm) and pulsed indium gallium arsenide (InGaAs, 905 nm) laser energy induced significantly faster return to function, recovery of muscle mass, and myelination of regenerated fibers.[14] One study suggested superior recovery after rat sciatic nerve crush injury when NIR diode laser treatment was delayed by seven days.[15] Consistent with findings from animal studies, multiple authors have suggested CW NIR diode lasers may provide clinical benefit in treating postsurgical paresthesia.[16-20]

Unlike HeNe and diode lasers, neodymium-doped yttrium aluminum garnet (Nd:YAG, 1064 nm) laser systems utilize pulse durations on the order of hundreds of microseconds (typically 100 to 650 µs). In animal and in vitro studies, pulsed Nd:YAG laser energy appears to consistently produce dose-dependent changes in sensory and motor nerve compound action potentials (CAPs).[21-24] Nevertheless, clinical outcomes following Nd:YAG laser treatment of surgical nerve injuries have not been reported in the literature. The purpose of the present case series was to document clinical responses to Nd:YAG laser irradiation in three consecutive patients with altered neurosensory function following surgical procedures.

Methods & Case Series

All patients in this case series presented to the Department of Periodontics, Army Postgraduate Dental School, Fort Gordon, GA, and exhibited systemic and periodontal health. Each patient completed an informed consent process involving verbal and written components. The Human Protections Administrator at Dwight David Eisenhower Army Medical Center, Fort Gordon, GA, reviewed this case series on April 15, 2021, and determined this activity does not constitute research as defined in 32 CFR 219.102(d) and DoDI 3216.02.

Case 1: A male patient, aged 39 years, presented in June 2020 with neurosensory deficits related to orthognathic surgery completed in May 2018. The patient reported numbness from the upper and lower lips, the mental region, and the anterior teeth and gingiva. On examination, the extraoral area of hypoesthesia extended superiorly beyond the base of the nose and laterally beyond the nasolabial fold. Inferiorly, the affected area extended to within 1 cm of the thyroid cartilage (Figure 1). Intraoral

hypoesthesia involved the anterior facial gigiva and alveolar mucosa, including the labial vestibule in the interforaminal region. We applied Nd:YAG laser energy to affected areas over four separate appointments (Table 1). In each session, we limited the cumulative dose to ≈2700 J intraorally and ≈4400 J extraorally. During intraoral and extraoral photobiomodulation, the optical fiber remained ≈2.5 to 3.5 cm and ≈3.5 to 6 cm from the tissue surface, respectively (Figs. 2 and 3). We applied the laser output using a deliberate overlapping circular motion.

The patient did not experience a complication following any laser session. Two months following treatment, we noted substantial improvement in sensation from the patient's neck and left perioral skin, compared with the baseline deficit mapping (Figure 1). Minimal extraoral changes occurred on the right side. The patient regarded intraoral improvements as the most noteworthy, citing particularly the recovery of sensation of the labial mucosa against the maxillary incisor teeth.

Table 1. Laser parameters and cumulative doses applied in each case.

Case	Injury Description	Time between Injury and Laser Application	Solid State Nd:YAG Laser Treatment Parameters	Laser Applications and Cumulative Doses [J]	Patient-Reported Sensation during Laser Application	Outcome Summary
1	Bilateral hypoesthesia following orthognathic surgery involving the peri-oral skin as well as the anterior teeth, facial gingiva, and alveolar mucosa	≈ Two years	Wavelength 1064 nm 360-µm optical fiber Pulse duration 100 µs Repetition rate 20 Hz **IO parameters** Pulse energy 150 J Average power 3.0 W Peak power 1500 W Irradiance 2947 W/cm^2 Fluence 147 J/cm^2 **EO parameters** Pulse energy 300 J Average power 6.0 W Peak power 3000 W Irradiance 5895 W/cm^2 Fluence 295 J/cm^2	First application: 7,200 J IO: 2,700 J EO: 4,500 J Second application: 7,207 J IO: 2,700 J EO: 4,507 J Third application: 7,103 J IO: 2,700 J EO: 4,403 J Fourth application: 7,111 J IO: 2,707 J EO: 4,404 J Total cumulative dose: 28,621 J	Minimal sensation at first application. Increased tingling and intermittent electric sensations at subsequent applications	Near complete recovery of neurosensory function from facial gingiva. Recovery of sensation from the labial mucosa against the maxillary incisor teeth was most noteworthy to the patient. Improvement in sensation from the patient's mental region and left perioral skin. Minimal extraoral changes on the right side
2	Paresthesia from the lower lip (right commissure to midline) following SFOT #20-29	One week		IO: 601 J EO: 1,201 J Total cumulative dose: 1,802 J	Tingling	Complete recovery of neurosensory function within two weeks of laser biostimulation
3	Hypoesthesia on the left side following orthognathic surgery involving the anterior mandibular teeth, gingiva, and alveolar mucosa, as well as the skin of the lower lip and mental region	Eight months		First application: 3401 J IO: 1,077 J EO: 2,324 J Second application: 6013 J IO: 1,001 J EO: 5,012 J Third application: 1351 J IO: 351 J EO: 1,000 J Total cumulative dose: 10,765 J	Prickling and electrical sensations	Complete recovery of intraoral neurosensory function. Increased sensation from perioral skin, left side

Nd:YAG = neodymium-doped yttrium aluminum garnet; IO = intraoral, EO = extraoral, SFOT = surgically facilitated orthodontic therapy

Figure 2. Intraoral biostimulation. The 360-µm optical fiber remained ≈2.5 to 3.5 cm from the tissue surface, and the operator applied laser energy in a deliberate overlapping circular motion (1064 nm, 3.0 W, 100 µs, 20 Hz). The target intraoral cumulative dose, applied across the anterior maxilla, was 2700 J per session.

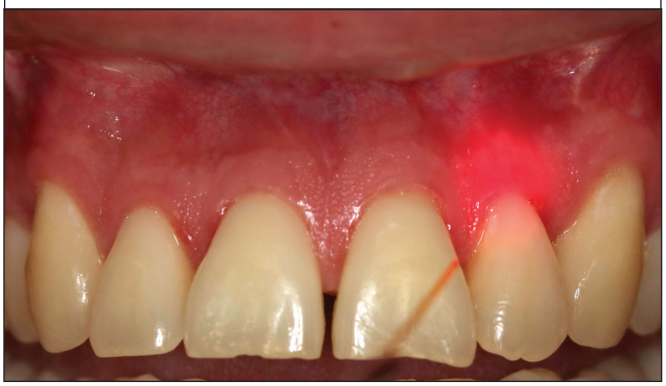
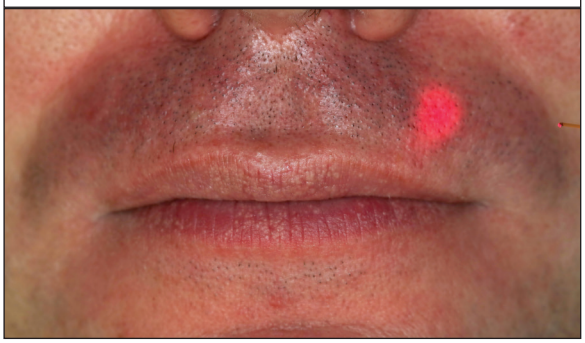


Figure 3. Extraoral biostimulation. The 360-µm optical fiber remained ≈3.5 to 6 cm from the tissue surface, and the operator applied laser energy in a deliberate overlapping circular motion (1064 nm, 6.0 W, 100 µs, 20 Hz). The target intraoral cumulative dose, applied across the affected area, was 4400 J per session.



Case 2: The Department of Orthodontics referred a 26-year-old female for surgically facilitated orthodontic treatment (SFOT) in March 2020. The patient exhibited dentoalveolar extrusion of mandibular incisors and recession type 1 (RT1) defects (<1mm) at teeth #23, 24, and 26 (Figure 4). The treatment plan consisted of periodontal phenotype conversion through SFOT, then subepithelial connective tissue grafts upon completion of the orthodontic phase. To access the alveolar bone, we reflected full thickness facial and lingual flaps from tooth #19 through 30, avoiding flap reflection on the lingual aspect of the central incisors. We made corticotomies adjacent to the roots of the canines and premolars bilaterally, penetrating into the cancellous bone (Figure 5). In the incisor area, we placed more superficial facial corticotomies where bone thickness and interdental space permitted. A solvent-dehydrated bone allograft (Puros Cortico-cancellous Particulate Allograft, Zimmer Biomet, Warsaw, IN) was applied (Figure 6), and the site was closed. At postoperative week one, the patient reported slight numbness and tingling of the lower lip (right commissure to midline). We applied Nd:YAG laser energy (Figures 7 and 8; Table 1), and at postoperative week three, sensation from the perioral skin had returned to normal.

Figure 4. Baseline appearance. Patient exhibited slight dentoalveolar extrusion of mandibular incisors, thin periodontal phenotype, and slight recession type 1 (RT1) defects (<1 mm) at teeth #23, 24, and 26. Treatment plan: phenotype conversion by surgically facilitated orthodontic therapy, with subepithelial connective tissue grafts upon completion of the orthodontic phase.

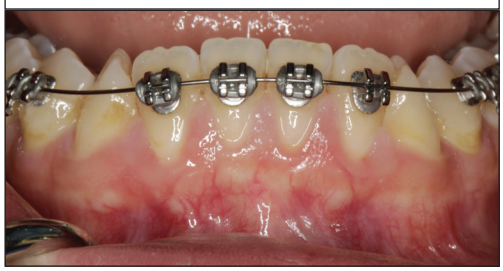


Figure 5. Corticotomies were placed adjacent to the roots of the canines and premolars bilaterally, penetrating into the cancellous bone. The incisor area received more superficial facial corticotomies where bone thickness and interdental space permitted.

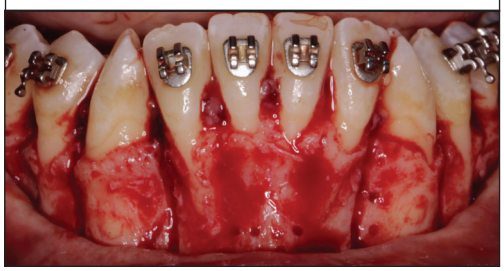


Figure 6. Application of a solvent-dehydrated bone allograft. Did not utilize a barrier membrane and elected to avoid a periosteal releasing incision, with connective tissue grafts intended upon completion of the orthodontic phase.

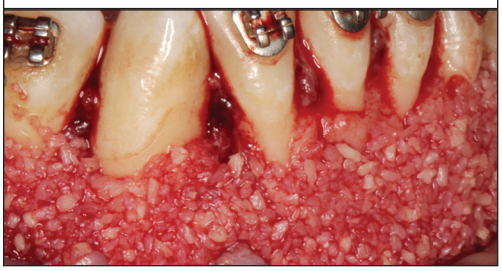


Figure 7. Extraoral biostimulation one week following surgery. Patient reported paresthesia involving the lower lip (right commissure to midline), presumably due to pressure from the graft and swelling against the mental nerve. During laser biostimulation, patient experienced tingling sensation. Complete recovery of neurosensory function was observed two weeks following biostimulation.

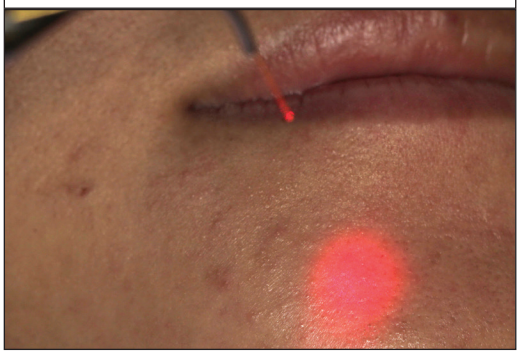
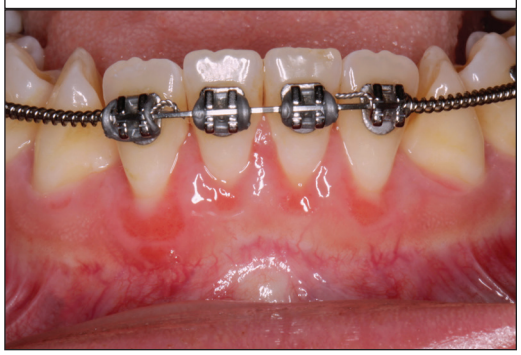
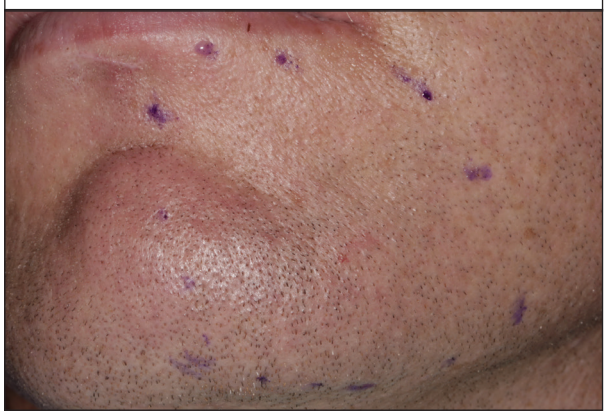


Figure 8. Clinical appearance three months following surgically facilitated orthodontic treatment. Normal neurosensory function was maintained.



Case 3: In August of 2018, a 34-year-old male patient with history of orthognathic surgery presented for evaluation and treatment of gingival recession defects at maxillary anterior and premolar sites. The patient reported diminished sensation from the left side of his chin and lower lip since orthognathic surgery in December 2017 (Figure 9). Intraorally, the hypoesthesia involved the mandibular teeth, gingiva, and alveolar mucosa anterior to the left mental foramen. Nd:YAG laser photobiomodulation was applied in three sessions (Table 1). Treatment resulted in complete recovery of neurosensory function at intraoral sites and partial return of sensation from the perioral skin.

Figure 9. Baseline neurosensory deficit mapping. Patient reported left-sided peri-oral numbness extending from his lower lip to the inferior border of the mandible since December 2017. Intraorally, mandibular teeth, gingiva, and alveolar mucosa anterior to the left mental foramen exhibited hypoesthesia.



Discussion

Our purpose was to document clinical responses to Nd:YAG laser irradiation in patients with surgical injury to terminal branches of the trigeminal nerve. Although clinical studies have reported NIR diode laser treatments may improve neurosensory function following surgical injury to cranial nerve V,[16-20] Nd:YAG laser use for this purpose is not previously reported in the literature. Our clinical observations appear consistent with prior suggestions that Nd:YAG laser output may modify neurophysiological responses to stimuli and hasten recovery of neurosensory function following injury.[21-24]

Although we did not compare the described Nd:YAG laser protocol with controls or alternative therapies, the laser parameters we applied were unique, with observed effects differing from those previously reported. The optical fiber we used to deliver laser energy was 360 microns in diameter, and for intraoral treatments, we set the average power at 3.0 W. Thus, the calculated irradiance at the fiber tip was extremely high (Table 1). Furthermore, the short pulse width we utilized (100 µs) resulted in high peak power attained during each pulse—1500 W during our intraoral applications. In contrast, the CW lasers utilized in some previous studies reached peak power values ≤70 mW.[6] Consistent with clinical observations from diode laser studies,[16-20] our patients experienced partial neurosensory recovery after Nd:YAG laser therapy. Unlike individuals receiving diode laser treatment,[20] each of our patients reported tingling or electrical sensations during noncontact laser energy application (Table 1). This observation probably has no clinical significance. However, sensation during treatment supports the hypothesis higher peak power and irradiance may permit photophysical and photochemical effects deeper within the tissue.

NIR lasers lose ≈50% power at a tissue depth of 4 mm, yet an energy density of 1 to 4 J/cm^2 at the target volume—the injured nerve—has been suggested as a PBM threshold.[25] The inferior alveolar nerve, which was affected in all three of the presented cases, courses within the body of the mandible, then enters soft tissue at the mental foramen. Obviously, our clinical protocol did not permit recording energy density at the target volume, and the degree to which surrounding bone and soft tissue attenuated the laser energy is unknown. Additionally, due to the distance between the optical fiber tip and the patient in our noncontact treatment protocol, beam divergence influenced the effective spot size at the tissue surface. Thus, irradiance values at the fiber tip and the tissue surface were nonequivalent. Furthermore, very small spot sizes give the impression of excessive irradiance, even with a modest "dose" to the patient.[8] Notably, biphasic responses to laser energy have been documented across a range of experimental conditions.[8,26,27] High irradiance does not necessarily assure favorable photochemical/photophysical responses.

Despite several decades of interest in laser-stimulated nerve regeneration, controlled clinical studies validating this therapy and optimizing dosimetry are lacking. Such studies are inherently difficult to control, because surgical and traumatic nerve injuries vary widely in severity and complexity. Multiple irradiation parameters—such as wavelength, average power, peak power, pulse duration, repetition rate, fluence, irradiance, cumulative dose, target volume, and number/timing of laser treatments—also undoubtedly influence tissue effects, promoting heterogeneity among studies. Clinical PBM research should focus narrowly on specific medical purposes, and results may not generalize beyond the limits of the experimental design. Such studies must remain well-controlled, with all relevant laser parameters

clearly documented.[28,29] Studies comparing NIR diode and Nd:YAG lasers in the described context appear warranted.

Conclusion

Few previous studies address the capacity for NIR laser energy to improve neurosensory function following surgical injury to the trigeminal nerve, and no study has documented Nd:YAG laser effects in this clinical scenario. Although our consecutive case series was not controlled, several conclusions appear justified:

- Patients with diminished neurosensory function appear to experience tingling or electrical sensations during noncontact Nd:YAG laser treatment. This effect may become more prominent with repeated laser applications.
- Among our patients, extraoral improvements tended to lag behind intraoral recovery of neurosensory function.
- Improvement in neurosensory function is possible, even when the deficiency is long-standing (up to two years).

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Authors

CPT Sarah M. Vargas serves as Resident, Department of Periodontics, Army Postgraduate Dental School, Uniformed Services University of the Health Sciences, Fort Gordon, GA.

CPT Megan E. Bunting serves as Resident, Department of Periodontics, Army Postgraduate Dental School, Uniformed Services University of the Health Sciences, Fort Gordon, GA.

CPT Richard B. Hill serves as Resident, Department of Periodontics, Army Postgraduate Dental School, Uniformed Services University of the Health Sciences, Fort Gordon, GA.

COL Douglas D. Lancaster serves as Program Director, US Army Advanced Education Program in Periodontics and Associate Professor, Department of Periodontics, Army Postgraduate Dental School, Uniformed Services University of the Health Sciences, Fort Gordon, GA.

COL Thomas M. Johnson serves as Professor, Department of Periodontics, Army Postgraduate Dental School, Uniformed Services University of the Health Sciences, Fort Gordon, GA.

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Sternal Gap Syndrome Caused by Improperly Fitted Body Armor: A Preventable Military Injury

Arada Wongmek, MD
Darine Kassar, MD
Matthew Parry, MC, MD
Shawna Scully, MC, DO

Abstract

Isolated atrophy of the pectoralis major muscle (PMM) secondary to traumatic lesion of the medial pectoral nerve is a known entity in the field of neuromuscular electrodiagnostics. Recent literature has begun describing a Pectoral Gap Phenomenon in which this atrophy occurs bilaterally as an overuse injury, leading to a marked concavity in the central chest wall musculature. While there is limited information in science journals on this topic, social media posts on weight lifting discuss the topic frequently. We report a case in which a soldier's body armor crushed the lateral medial and pectoral nerves against the anterior chest wall causing permanent upper body weakness. To optimize military medical readiness, awareness of this disorder and the pathophysiology causing it should spread so as to mitigate this potential for significant disability.

Keywords: bilateral pectoralis major atrophy, body armor, pectoral gap syndrome, Steinert syndrome

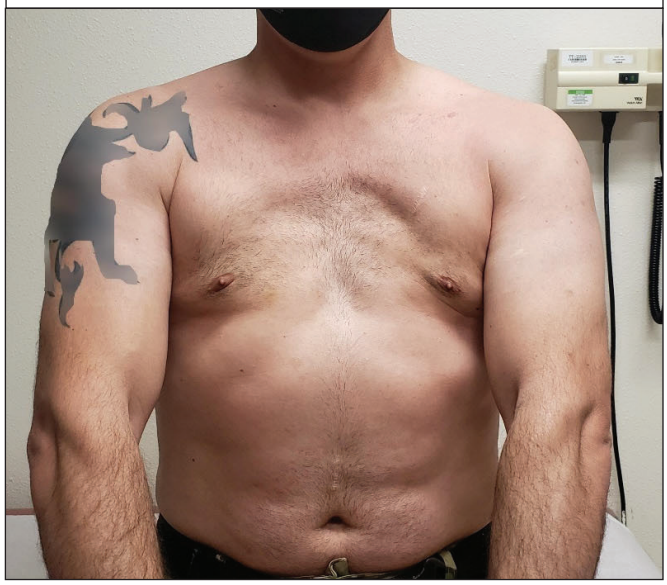
Case Report

A 39-year-old, right-hand dominant male presented with bilateral medial pectoral atrophy, which began during his 2018 Middle East deployment. He started wearing body armor during all training exercises and physical fitness routines three months prior to deployment, and wore the vest on an almost daily basis while on combat missions for the next 8 months in theater. He typically wore size extra large shirts and a large flak vest, explaining that flight crews in helicopters wore one size smaller vest than they normally wore in a shirt to keep things snug and avoid catching on equipment in the cockpit (Figure 1). Upon deployment he was given a new vest that was not broken in, along with a flight vest cinched down over the body armor. All of this restricted his movement to some extent and caused muscle soreness in the anterior axillary folds. Over time, he noted loss of muscle mass in the center of his chest along with upper body weakness that he attributed to spending less time in the gym for workouts.

During deployment he experienced no known injuries to the chest wall, brachial plexii, or cervical region and reported no significant illness or infection. He denied any cramping, fasciculations, or other atypical motor activity. He redoubled his physical fitness efforts but experienced progression of the muscle wasting and weakness along with the development of tenderness to palpation in the region of the chest underlying the atrophy, which made wearing body armor extremely uncomfortable. He ceased all upper body weight training but noted no improvements. Once he returned from deployment and didn't have to wear his protective gear as frequently, the pain improved slightly (persisting at 6/10 to any application of pressure, 0/10 at rest), but the weakness and atrophy remained (Figure 2).

Figure 1. Patient wearing his flak vest.

Figure 2. Patient's pectoral gap.

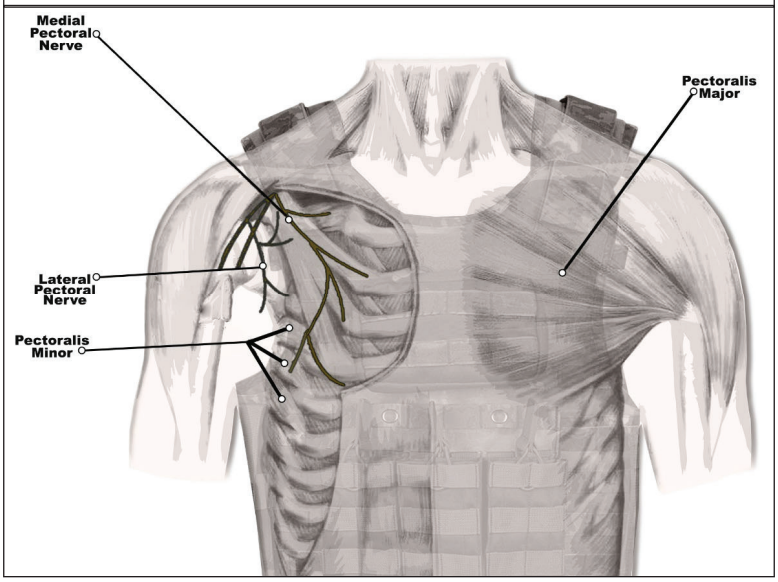


The patient was referred to neurology where a physical exam revealed no deficits aside from left-greater-than-right wasting of the inferior sternal divisions of the bilateral pectoralis major muscles (PMM). This was associated with 3/5 weakness of humeral adduction and internal rotation. Deep tendon reflexes were 2+ throughout in the upper and lower extremities. He reported no family history of neuromuscular disease, and no significant past medical or surgical history, aside from left mastectomy in 2011 to manage gynecomastia. After that surgery, no focal deficits were appreciated. Magnetic resonance imaging (MRI) of the brain, cervical spine, and brachial plexus identified no abnormalities. Basic labs to include a complete blood count (CBC), renal panel, thyroid panel, and inflammatory markers were all within normal limits.

On electrodiagnostic testing, the bilateral median, ulnar, and radial nerves demonstrated normal sensory and motor responses including F-waves. Studies of the medial and lateral antebrachial nerves were normal as well. Motor responses of bilateral pectoral nerves stimulated at Erb's point and recorded from the pectoralis major muscles were absent. Concentric needle electromyography (EMG) showed positive sharp waves and fasciculations on the left PMM. EMG of the PMM, left deltoid, bilateral biceps, left supraspinatus, bilateral first dorsal interosseii, left abductor pollicis brevis, left flexor carpi ulnaris, left pronator teres, and left cervical paraspinal musculature were all within normal limits.

The patient's history, clinical course, and electrodiagnostic findings confirmed bilateral left-greater-than-right medialpectoral neuropathy leading to atrophy of the inferior sternal divisions of both pectoralis major muscles, otherwise known as pectoral gap syndrome.

Figure 3. Diagram of pectoral anatomy with flak vest overlay.



Discussion

The medial pectoral nerve exits from the medial cord of brachial plexus. It runs along the lower border of the pectoralis minor muscle (PmM), which it pierces and supplies, proceeding to innervate the sternal border of the PMM (Figure 3). In cases of bilateral pectoral muscle atrophy, the differential diagnosis ranges from

brachial plexopathy, radiculopathy, neuropathy, or even a myopathy. In our case, brachial plexopathy and cervical radiculopathy were excluded based on negative imaging and EMG results that revealed no evidence of neuropathic compromise in the brachial plexus and cervical myotomes. Electrodiagnostics instead demonstrated absent motor responses of the bilateral pectoral nerves along with an isolated neurogenic process affecting the sternal portion of the left PMM, indicating severe damage to the left medial pectoral nerve.

Isolated atrophy of the PMM secondary to lesion of the pectoral nerve is a known entity in electodiagnostic literature. Unilateral cases have typically been attributed to focal trauma, like seatbelt injury during a motor vehicle accident.[3] There is also a case of iatrogenic pectoral gap syndrome incurred during thoracic endoscopic sympathectomy.[2] Recent literature has begun describing a Pectoral Gap Phenomenon, in which this atrophy occurs bilaterally. The few reported cases of bilateral PMM atrophy have been attributed to breast reconstruction surgery, and in sports medicine literature, to entrapment of the medial pectoral nerve as it passes through a hypertrophied PmM. Some have also postulated "chronic injury and/or micro trauma of the pectoral region resulting from constant workouts and/or impacts from an opponent in competition" as a contributor to this condition.[1,4,5] Of note, while there are few scientific articles on this topic, social media posts on body building reference this frequently.[6,7]

This case represents, to the best of our knowledge, the first confirmed report of pectoral gap syndrome secondary to a bilateral neural compression injury. As the condition can result in upper body weakness and chronic pain that precludes wear of body armor, it is important for the military community to be aware of this phenomenon and ensure steps are taken to avoid it, such as ensuring flak vests are properly sized.

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