ORIGINAL RESEARCH

Prehospital Tourniquet Usage and Diabetes Mellitus Associated with Increased Incidence, Odds, and Risk of Acute Kidney Injury: A Pilot Study

Roland Paquette, PA-C, MPAS;[1] David Wampler, PhD;[2] Randall Schaefer, DNP, RN;[3] Ashlee Blume, PA-C, MPAS;[4] Holly Casillas, PA-C, MPAS;[4] Briana Echols, PA-C, MPAS;[4] Katelyn Greene, PA-C, MPAS;[4] Mallory McFarland, PA-C, MPAS;[4] Paul Allen, PA-C, DSc[1]

1. Department of Physician Assistant Studies and Department of Emergency Medicine, University of Texas Health Science Center at San Antonio, San Antonio, Texas, USA
2. Department of Emergency Health Sciences, University of Texas Health Science Center at San Antonio, San Antonio, Texas, USA
3. Research Division Director, Southwest Texas Regional Advisory Council (STRAC), San Antonio, Texas, USA
4. Department of Physician Assistant Studies, University of Texas Health Science Center at San Antonio, San Antonio, Texas, USA

Correspondence:
Roland Paquette, PA-C
Department of Physician Assistant Studies
The University of Texas Health San Antonio
7703 Floyd Curl Drive Mail Code 6249
San Antonio, Texas 78229-3900 USA
E-mail: paquetteR@uthscsa.edu

Conflicts of interest/funding: The authors have no conflicts of interest to declare.

Keywords: acute kidney injury; advanced trauma life support; diabetes mellitus; prehospital emergency care; tourniquet

Abbreviations:
AKI: acute kidney injury
EMS: Emergency Medical Services
KDIGO: Kidney Disease: Improving Global Outcomes
STRAC: Southwest Texas Regional Advisory Council

Received: January 18, 2022
Revised: February 12, 2022
Accepted: February 21, 2022

doi:10.1017/S1049023X2200067X

Abstract

Introduction: Tourniquets are the standard of care for civilian and military prehospital treatment of massive extremity hemorrhages. Over the past 17 years, multiple military studies have demonstrated rare complications related to tourniquet usage. These studies may not translate well to civilian populations due to differences in baseline health. Experimental studies have demonstrated increased rates of post-traumatic acute kidney injuries (AKIs) in rats with obesity and increased oxidative stress, suggesting that comorbidities may affect AKI incidence with tourniquet usage. Two recently published retrospective studies, focused on the safety of tourniquets deployed within civilian sectors, documented increased incidence of AKI in patients with a prehospital tourniquet as compared to previously published military results. This study aimed to provide descriptive data concerning the association between the use of prehospital tourniquets and AKIs amongst civilian patient populations as AKIs increase mortality in hospitalized patients.

Methods: This was a single-center, observational, cross-sectional, pilot study involving chart review of participants presenting to a tertiary Level 1 trauma center. Patient data were extracted from prehospital and hospital electronic medical records. For this study, AKI was defined using the *Kidney Disease: Improving Global Outcomes* (KDIGO) guidelines.

Results: A total of 255 participants were included. Participants with a history of diabetes mellitus had a significantly higher incidence of AKI as compared to those without. Analysis revealed an increased odds of AKI with diabetes in association to the use of a prehospital tourniquet. Participants with diabetes had an increased relative risk of AKI in association to the use of a prehospital tourniquet. The incidence of AKI was statistically higher than what was previous reported in the military population in association with the use of a prehospital tourniquet.

Conclusion: The incidence of AKIs was higher than previously reported. Patients with diabetes had an associated higher risk and incidence of sustaining an AKI after the use of a prehospital tourniquet in association with the use of a prehospital tourniquet. This may be due to the known deleterious effects of diabetes mellitus on renal function. This study provides clinically relevant data that warrant further multi-site investigations to further investigate this study's associated findings and potential causation. It also stresses the need to assess whether renally-impacting environmental and nutritional stressors affect AKI rates amongst military personnel and others in which prehospital tourniquets are used.

Paquette R, Wampler D, Schaefer R, Blume A, Casillas H, Echols B, Greene K, McFarland M, Allen P. Prehospital tourniquet usage and diabetes mellitus associated with increased incidence, odds, and risk of acute kidney injury: a pilot study. *Prehosp Disaster Med.* 2022;37(3):360–364.

Introduction

Background

When appropriately applied to massive extremity hemorrhages, tourniquets have become an irrefutable life-saving intervention.[1–4] For this reason, tourniquets have become the standard of care for civilian and military prehospital treatment of massive extremity hemorrhages.[5–10]

A properly applied tourniquet stops all blood flow distal of the device via circumferential pressure. Multiple retrospective studies have been conducted examining the military's use of tourniquets in the last 17 years, demonstrating minimal complications related to tourniquet usage. Rare complications of tourniquet use in military populations include neuropathy, decreased limb function, amputation, and impaired kidney function.[1–3,11–17] Studies within military populations may not translate well to civilian populations due to differences in age, fitness, and baseline health. This disparity may apply to the most foundational of military research.

There have been civilian case reports of acute kidney injury (AKI) after tourniquet usage during surgical cases and experimental studies in which mice experience renal pathology.[18–23] Additionally, more recent studies have demonstrated increased rates of post-traumatic AKIs in rats with obesity and increased oxidative stress, both of which can be found in the civilian population.[24–28] Important health-related characteristics of the military population found within the previously mentioned studies that demonstrated minimal to no complications related to tourniquet usage may not reflect the population in which prehospital tourniquets are applied within the civilian sectors.[29] When prehospital tourniquets are applied to a civilian population with increased underlying risk factors such as obesity and medical illness, the complication rate could exceed studies in military populations. Specifically, the rates of associated AKI could be increased due to pre-existing renal stressors such as hypertension and diabetes mellitus in a population already prone to AKI due to injury-related hypovolemia and the need for necessary interventions that may adversely affect the kidneys.[30–32] If pre-existing conditions increased the risk of AKI after the use of a prehospital tourniquet, this would be of importance to clinical decision making as AKIs increase the likelihood of death up to four-times the baseline in hospitalized and critically injured patients.[33,34]

Two recently published retrospective chart reviews by Inaba, et al and Scerbo, et al documented incidental AKIs in trauma patients who received civilian prehospital tourniquets at a frequency of less than 3.2%.[35,36] After aggregating the incidence of AKI found by Inaba, et al (two out of 87; 2.3%) and Scerbo, et al (three out of 105; 2.9%), there was an aggregated incidence of five AKIs out of 192 (2.6%) civilian trauma patients.[35,36] Inaba, et al and Scerbo, et al did not examine patient characteristics that may increase tourniquet-associated complications, nor did they imply causation between tourniquet usage and AKI.[35,36] Yet, they provide an associated incidence of AKI with civilian tourniquet usage that surpassed previous results in the military population published by Kragh, et al (seven out of 427; 1.6%).[11]

Harrois, et al provided significant insight into the multifactorial pathophysiology of AKIs in trauma patients.[37] Iodinated contrast, inflammation, hemorrhagic shock, rhabdomyolysis, abdominal compartment syndrome, and fluid excess all increased the chances of an AKI.[37] Tourniquet usage could increase rhabdomyolysis and inflammation, which Harrois, et al further delineated as occurring at significantly higher levels during ischemia-reperfusion events.[37] In theory, tourniquet-related inflammation and muscular apoptosis with subsequent myoglobinemia could tip the scales into an AKI, even if neither event would cause an AKI when experienced in isolation. This additive and deleterious effect could be further increased in patients with renally-injurious comorbidities such as diabetes mellitus or hypertension.

This cross-sectional study aimed to provide descriptive data concerning AKI incidence and relative risk amongst civilian patients treated with at least one prehospital tourniquet. This study is not meant to affect the usage of tourniquets for massive extremity hemorrhages, nor imply causation, but to investigate a potential increased association demonstrated by Inaba, et al and Scerbo, et al that warrants further investigation.[35,36] The study hypothesized that renal comorbidities, such as diabetes mellitus and hypertension, would increase the incidence of associated AKIs in patients treated with a prehospital tourniquet.

Methods

Expedited study approval was obtained through the University of Texas Health Science Center San Antonio Office of Institutional Research, IRB (San Antonio, Texas USA) HSC20190008H; the University Hospital Research Office (San Antonio, Texas USA), 20190008H; and the US Army Medical Research and Development Command Human Research Protection Office (Fort Detrick, Maryland USA), 13293001, before initiation of the study. This study was conducted in support of the "Remote Trauma Outcomes Research Network (RemTORN): A Civilian Research Model for Translation to Military Pre-Hospital Care." As this was a retrospective chart review, human research participant consent was waived by the review boards.

Study Design

This was a single-center, observational, retrospective, cross-sectional pilot study involving chart review of patients presenting to University Hospital (San Antonio, Texas USA), a tertiary Level 1 trauma center, after having at least one tourniquet applied by prehospital personnel. This study's desired outcome was to identify the incidence of an AKI after using at least one prehospital tourniquet and to identify potential predisposing factors that may be associated with an increased incidence and risk of AKI.

Selection of Participants

Patients with prehospital tourniquet usage transported to University Hospital were identified within the multi-Emergency Medical Service (EMS) agency electronic record system maintained by the Southwest Texas Regional Advisory Council's (STRAC) EMS Electronic Patient Care Record. Patient-related data were then used to match patients within the University Hospital's electronic medical record. All patient recorded as having a prehospital tourniquet and transported by EMS were captured within this study. Patients that were received with generic "John Doe" identifiers were found within the hospital records using the transport date, time, gender, and injuries as identifiers. Inclusion criteria required the application of at least one tourniquet in the prehospital environment and an age of at least 18 years old. Participants identified as prisoners, pregnant, on hemodialysis, deceased before EMS transport, deceased during the initial resuscitation, and those in which a thoracotomy was performed were excluded from the study.

Measurement and Outcomes

Patient data were extracted from the prehospital and hospital electronic medical records. Inter-rater reliability and precision were achieved with an independent review of 25% of charts. The STRAC prehospital database contains patients transported by EMS in the South Texas region to the hospital used in this study. Using the data gathered at pre-designated time intervals and an approved surrogate value for baseline creatinine when actual baseline creatinine was not available, it was determined whether the patient experienced an AKI after applying a prehospital tourniquet. Consistent with other previously published studies, the surrogate baseline creatinine level was obtained from the *Estimated Baseline*

https://doi.org/10.1017/S1049023X2200067X Published online by Cambridge University Press

Mean Age (years)	38.6 (SD = 15.6)
Sex	
Male	200 (78.4%)
Female	55 (21.6%)
Indication for TQ	
Laceration	122 (47.8%)
Gun Shot Wound	53 (20.8%)
Unknown	35 (13.7%)
Open Fracture	14 (5.5%)
Other Penetrating Injury	11 (4.3%
Partial Amputation	8 (3.1%)
Amputation	6 (2.4%)
Crush Injury	5 (2.0%)
Snake Bite	1 (0.4%)
Location of TQ	
Upper Extremity (UE)	124 (48.6%)
Lower Extremity (LE)	86 (33.7%)
Unknown	39 (15.3%)
Bilateral LE	3 (1.2%)
Bilateral UE	2 (0.8%)
UE & LE	1 (0.4%)

Table 1. Participant Characteristic
Abbreviations: AKI, acute kidney injury; TQ, tourniquet.

SCr Based on Modification of Diet in Renal Disease (MDRD) study.[38–40] For this study, AKI was defined using the validated guidelines provided by the *Kidney Disease: Improving Global Outcomes (KDIGO)*.[34,41,42] Per KDIGO guidelines, an AKI is defined by an increase in serum creatinine by ≥ 0.3mg/dL (≥ 26.5micromol/L) within 48 hours or an increase in serum creatinine to ≥ 1.5-times baseline, which is known or presumed to have occurred within the prior seven days, or urine volume < 0.5mL/kg/hour for six hours. Individual components of the KDIGO guidelines were extracted from the patient records. In addition to the continuous data, a dichotomous AKI indicator (yes or no) was determined using the KDIGO guidelines. Blank or missing information related to the KGIDO guidelines or other data extraction points were left blank and considered null towards qualifying whether an AKI occurred.

Statistical Analysis

Statistical analysis was conducted using IBM SPSS version 26 (IBM; Armonk, New York USA). Analyzing the presence of an AKI involved the use of a two-tailed Pearson Chi-Square test. A z-test comparison of column proportions and Bonferroni adjusted P values was used to prevent Type I error while analyzing the participants' comorbid conditions, such as diabetes and hypertension. Participant ages amongst those with AKI and those without was compared with independent t-tests to control for the confounder of age. The data were further analyzed using odds ratios and relative risk with 95% confidence intervals (CI).

Results

From March 2009 through June 2019, 313 records were identified within the prehospital STRAC database that included the use of at least one tourniquet. After applying the inclusion and exclusion criteria, 255 participants were included in this study, with characteristics shown in Table 1.

Count		AKI Yes	AKI No	Total
History of Diabetes	Yes	5	24	29
	No	12	214	226
Total		17	238	255

Table 2. Diabetes and AKI
Abbreviation: AKI, acute kidney injury.

Mean Age (years)	50.21 (SD = 20.1)
Sex	
Male	13 (76.5%)
Female	4 (23.5%)
Indication for TQ	
Laceration	6 (35.2%)
Gun Shot Wound	3 (17.6%)
Unknown	4 (23.5%)
Open Fracture	4 (23.5%)
Location of TQ	
Upper Extremity (UE)	7 (41.2%)
Lower Extremity (LE)	7 (41.2%)
Unknown	3 (17.6%)

Table 3. Characteristic of Participants with AKI
Abbreviations: AKI, acute kidney injury; TQ, tourniquet.

Among the 29 participants with known diabetes mellitus, five (17.2%) experienced an AKI. Participants with a history of diabetes mellitus had a significantly higher incidence of AKI as compared to those without diabetes (12 out of 226; 5.3%; X^2[1, N=255, 5.881]; adjusted P = .031; Table 2). The analysis demonstrated no difference in the incidence of AKI without diabetes mellitus (12 out of 226) as compared to the previously published and aggregated civilian data published by Inaba, et al and Scerbo, et al (five out of 192; 2.6%; X^2[1, N=418, 1.316]; P = .251).[35,36] The characteristics of the participants who experienced an AKI in association with the use of a prehospital tourniquet are shown in Table 3. Those who experienced an AKI had a higher incidence of open fractures (four out of 17) compared to the overall group (14 out of 255; X^2[1, N=272, 8.545]; P = .003). No other differences were found within the categorical characteristics of those with and without an AKI. The mean ages of those with (44.41; SD = 19.11) and without diabetes mellitus (64.60; SD = 15.40) that had an associated AKI were not statistically different (t [15] = -2.084; P = .055) with equal variances due to non-significant Levene's Test of homogeneity. Forty-five participants had a documented history of hypertension and twenty participants were documented to have both diabetes mellitus and hypertension. There was no difference in the incidence of AKI in those with hypertension or diabetes mellitus and hypertension (X^2[1, N=255, 3.903]; P = .090 and X^2[1, N=255, 2.422]; P = .138).

Odds ratio analysis revealed an increased odds of AKI with a known history of diabetes mellitus in association with the use of a prehospital tourniquet (OR = 3.715; 95% CI, 1.206 - 11.448). Participants with known diabetes had an increased relative risk of AKI associated with the use of a prehospital tourniquet (RR = 3.247; 95% CI, 1.232 - 8.557; Figure 1).

https://doi.org/10.1017/S1049023X2200067X Published online by Cambridge University Press

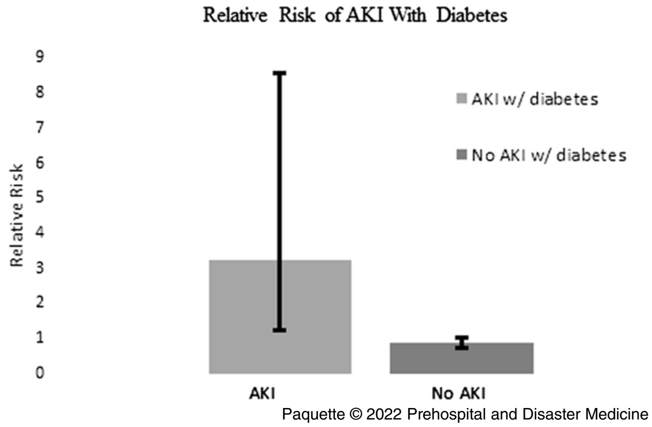

Figure 1. Relative Risk of AKI with Diabetes Mellitus and Prehospital Tourniquet Use.
Abbreviation: AKI, acute kidney injury.

Analysis revealed that 17 of the 255 (6.67%) included participants experienced an AKI associated with using a prehospital tourniquet. An analysis using the aggregated civilian incidence published by Inaba, et al and Scerbo, et al (five out of 192; 2.6%) demonstrated no statistically higher incidence of AKI amongst this study's participants in association with the use of a prehospital tourniquet (X^2[1, N=447, 3.044]; P = .081).[35,36] Yet, the incidence of AKI amongst the included participants was statistically higher than what was previously reported in the military population by Kragh, et al (seven out of 427; 1.6%; X^2[1, N=682, 10.450]; P = .001) in association with the use of a prehospital tourniquet.[11]

Discussion

Within the included participants, those with a known history of diabetes mellitus experienced a higher incidence of AKI, in association with the use of a prehospital tourniquet, compared to those without the disorder. Participants with a known history of diabetes mellitus also had an increased incidence of AKI, in association with using a prehospital tourniquet, compared to previously published incidence data.[35,36] Additionally, participants with a known history of diabetes mellitus had an increased odds ratio and relative risk of AKI associated with the use of a prehospital tourniquet. There is no causality to be inferred from this descriptive, retrospective study. However, the increased incidence, odds, and risk of AKI found in this study's participants with a known history of diabetes mellitus in association with the use of a prehospital tourniquet does raise the question as to whether the well-documented cumulative and deleterious effects of diabetes mellitus on the renal system can increase the incidence of AKI after a traumatic injury requiring a prehospital tourniquet.[30,32] The baseline renal glomerular changes associated with diabetes mellitus could increase AKI incidence when a person's kidneys are faced with potentially deleterious trauma-related factors.[30–32,37]

The overall incidence of AKI amongst the included participants was statistically higher than the previously published data by Kragh, et al.[11] This significant difference could be due to the previously described deleterious effects of diabetes on baseline renal health and the increased incidence of diabetes amongst this study's participants compared to the military.[30–32] The incidence of diabetes mellitus within this study's participants was 29 out of 255 (11.4%). The incidence of diabetes mellitus in the deployed military population, in which the previously published data were collected by Kragh, et al, could be considered non-existent due to its presence preventing deployment.[43] It could therefore be hypothesized that the increased presence of diabetes mellitus could account for the increased incidence of AKIs found in civilians as compared to military patients, in association with the use of a prehospital tourniquet. There was no difference in the incidence of AKI between this study's participants and the incidence reported by Inaba, et al and Scerbo, at al.[35,36] The incidence of diabetes mellitus amongst the participants resulted in Inaba's, et al and Scerbo's, et al studies were not reported. Therefore, similar comparisons concerning the incidence of diabetes mellitus could not be calculated, nor could its association with their participants developing an AKI be evaluated to refute or support this study's findings.[35,36]

This pilot study provides novel results into prehospital tourniquet use and associated incidence of AKIs from those previously published using military populations. It cannot be stressed enough that this study is not meant to affect prehospital tourniquet usage, as it is a life-saving intervention. In this vain, the new data found within this pilot study warrant further investigation. Additional multi-center studies would support or refute this single-center pilot study and increase the availability of clinically relevant information to receiving emergency staff to recalibrate their suspicion that a patient with diabetes and a prehospital tourniquet could develop an AKI and increase their mortality.

Limitations

There are several limitations centered around the retrospective nature of records, such as the accuracy and completeness of the databases and the ability to control for potential confounders. The STRAC prehospital database contains all patients transported by EMS to the hospital studied. The prehospital patient care record requests that responding EMS professionals document either the presence of a tourniquet prior to their arrival or if EMS placed a tourniquet during treatment and transport to the receiving University Hospital. It is possible that under the circumstances of severe trauma, a patient's entire medical history was not solicited and, therefore, it was not complete. It is also possible that patients with a prehospital tourniquet were transported by personal vehicle to the receiving hospital, which would have prevented this study from capturing their medical data.

This study sought to find whether a patient experienced an AKI in association with using a prehospital tourniquet within 48 hours of the injury. It is possible that the medical record did not reflect a transient AKI in the participants' records because the appropriate laboratory study was not conducted during the period of renal insult. Some of the included records were also found to be missing accurate measurements of urine output. While one would assume that oliguria or anuria would have been reflected in the participants' records, this cannot be guaranteed. If these limitations did affect the resultant data, it would have biased the data in favor of fewer incidence of AKIs and the acceptance of the null hypothesis, which was not the case in this study. Likewise, single-center data provides well-known limitations. This study did not factor in hemorrhagic shock's effect on renal function and the subsequent increased risk of AKI. Yet, the effect of exsanguination and hypovolemic shock would have been theoretically distributed across all the included participants.

Within this study, participants with an open fracture were over-represented amongst those who experienced an AKI compared to the overall participant pool. This difference could indicate that the pathology involved in an open fracture increased participants' chances of experiencing an AKI, confounding this analysis. While the other characteristics were found to be similar (Tables 2 and 3), there was limited ability to control for other potential confounders.

Conclusion

This study revealed new information regarding AKIs associated with prehospital tourniquets in patients with diabetes mellitus. This area of research warrants further investigation with a large multi-center retrospective study or one of a prospective nature spanning geographic regions to further investigate the potential impact of diabetes mellitus and prehospital tourniquet use on renal function. The proposed study may also be beneficial to investigate whether renally impacting environmental and nutritional stressors can lead to increased incidence and prevalence of AKIs amongst military personnel who receive a prehospital tourniquet.

Acknowledgement

The authors would like to acknowledge Lawrence Roakes and his essential data extraction from the STRAC record system, without which this study would not have been possible.

References

1. Butler FK. TCCC updates: two decades of saving lives on the battlefield: tactical combat casualty care turns 20. *J Spec Oper Med.* 2017;17(2):166–172.
2. Eastridge BJ, Mabry RL, Seguin P, et al. Death on the battlefield (2001-2011): implications for the future of combat casualty care. *J Trauma Acute Care Surg*. 2012; 73(6 Suppl 5):S431–437.
3. Kotwal RS, Montgomery HR, Kotwal BM, et al. Eliminating preventable death on the battlefield. *Arch Surg.* 2011;146(12):1350–1358.
4. Kragh JF Jr., Dubick MA, Aden JK, et al. US Military use of tourniquets from 2001 to 2010. *Prehosp Emerg Care.* 2015;19(2):184–190.
5. Committee For Tactical Emergency Casualty Care. Tactical Emergency Casualty Care (TECC) Guidelines for Active Bystanders. http://www.c-tecc.org/images/TECC_Guidelines_for_Active_Bystanders_Final_2020_1_2_copy.pdf. Published 2020. Accessed January 14, 2022.
6. Committee on Tactical Combat Casualty Care. TCCC Guidelines 2021. Joint Trauma System. https://deployedmedicine.com/content/40. Accessed January 14, 2022.
7. Jacobs L, Burns KJ. The Hartford Consensus to improve survivability in mass casualty events: process to policy. *Am J Disaster Med.* 2014;9(1):67–71.
8. Committee on Tactical Combat Casualty Care. Tactical Combat Casualty Care for All Service Members. Defense Health Agency. https://books.allogy.com/web/tenant/8/books/8ab6b4fc-93e8-4a4b-ba26-c20668cb2f76/. Accessed January 14, 2022.
9. American College of Surgeons. Stop the Bleed. American College of Surgeons. https://www.stopthebleed.org/resources-poster-booklet. Accessed February 23, 2021.
10. American College of Surgeons. *Advanced Trauma Life Support (ATLS Student Course Manual, 10th Edition)*. Chicago, Illinois USA: American College of Surgeons; 2018: 151.
11. Kragh JF Jr., O'Neill ML, Walters TJ, et al. Minor morbidity with emergency tourniquet use to stop bleeding in severe limb trauma: research, history, and reconciling advocates and abolitionists. *Mil Med.* 2011;176(7):817–823.
12. Eastridge BJ, Hardin M, Cantrell J, et al. Died of wounds on the battlefield: causation and implications for improving combat casualty care. *J Trauma.* 2011;71(1 Suppl): S4–8.
13. Kragh JF Jr. Use of tourniquets and their effects on limb function in the modern combat environment. *Foot Ankle Clin.* 2010;15(1):23–40.
14. Kragh JF Jr., Dubick MA. Battlefield tourniquets: lessons learned in moving current care toward best care in an Army medical department at war. *US Army Med Dep J.* 2016(2–16):29–36.
15. Gerhardt RT, Berry JA, Blackbourne LH. Analysis of life-saving interventions performed by out-of-hospital combat medical personnel. *J Trauma.* 2011;71(1 Suppl): S109–113.
16. Kragh JF Jr., Walters TJ, Baer DG, et al. Survival with emergency tourniquet use to stop bleeding in major limb trauma. *Ann Surg.* 2009;249(1):1–7.
17. Lakstein D, Blumenfeld A, Sokolov T, et al. Tourniquets for hemorrhage control on the battlefield: a 4-year accumulated experience. *J Trauma.* 2003;54(5 Suppl): S221–225.
18. Orsi R, Brunelli G, Zorzi F. Lesions of the kidney in tourniquet shock: ultrastructural study. *Microsurgery.* 1984;5(4):191–196.
19. Shenton DW, Spitzer SA, Mulrennan BM. Tourniquet-induced rhabdomyolysis. A case report. *J Bone Joint Surg Am.* 1990;72(9):1405–1406.
20. Palmer SH, Graham G. Tourniquet-induced rhabdomyolysis after total knee replacement. *Ann R Coll Surg Engl.* 1994;76(6):416–417.
21. Sheth NP, Sennett B, Berns JS. Rhabdomyolysis and acute renal failure following arthroscopic knee surgery in a college football player taking creatine supplements. *Clin Nephrol.* 2006;65(2):134–137.
22. Turkmen I, Esenkaya I, Unay K, Akcal MA. Rhabdomyolysis after tourniquet use in proximal tibial osteotomy: a case report and review of the literature. *Acta Orthop Traumatol Turc.* 2015;49(3):338–341.
23. Vold PL, Weiss PJ. Rhabdomyolysis from tourniquet trauma in a patient with hypothyroidism. *West J Med.* 1995;162(3):270–271.
24. Mittwede PN, Xiang L, Lu S, Clemmer JS, Hester RL. A novel experimental model of orthopedic trauma with acute kidney injury in obese Zucker rats. *Physiol Rep.* 2013;1(5):e00097.
25. Palm F, Nordquist L. Renal oxidative stress, oxygenation, and hypertension. *Am J Physiol Regul Integr Comp Physiol.* 2011;301(5):R1229–1241.
26. Kashihara N, Haruna Y, Kondeti VK, Kanwar YS. Oxidative stress in diabetic nephropathy. *Curr Med Chem.* 2010;17(34):4256–4269.
27. Mittwede PN, Xiang L, Lu S, Clemmer JS, Hester RL. Oxidative stress contributes to orthopedic trauma-induced acute kidney injury in obese rats. *Am J Physiol Renal Physiol.* 2015;308(2):F157–163.
28. Xiang L, Thompson MS, Clemmer JS, Mittwede PN, Khan T, Hester RL. Early treatment with GLP-1 after severe trauma preserves renal function in obese Zucker rats. *Am J Physiol Regul Integr Comp Physiol.* 2019;316(5):R621–627.
29. Hoerster KD, Lehavot K, Simpson T, McFall M, Reiber G, Nelson KM. Health and health behavior differences: US Military, veteran, and civilian men. *Am J Prev Med.* 2012;43(5):483–489.
30. Hsu CY, Ordonez JD, Chertow GM, Fan D, McCulloch CE, Go AS. The risk of acute renal failure in patients with chronic kidney disease. *Kidney Int.* 2008;74(1): 101–107.
31. Huang TM, Wu VC, Young GH, et al. Preoperative proteinuria predicts adverse renal outcomes after coronary artery bypass grafting. *J Am Soc Nephrol.* 2011;22(1): 156–163.
32. Bargman JM, Skorecki KL. Chronic Kidney Disease. In: *Harrison's Manual of Medicine, 20e*. Twentieth Edition ed. New York USA: McGraw-Hill Education; 2018.
33. Bihorac A, Delano MJ, Schold JD, et al. Incidence, clinical predictors, genomics, and outcome of acute kidney injury among trauma patients. *Ann Surg.* 2010; 252(1):158–165.
34. Ulger F, Pehlivanlar Kucuk M, Kucuk AO, et al. Evaluation of acute kidney injury (AKI) with RIFLE, AKIN, CK, and KDIGO in critically ill trauma patients. *Eur J Trauma Emerg Surg.* 2018;44(4):597–605.
35. Inaba K, Siboni S, Resnick S, et al. Tourniquet use for civilian extremity trauma. *J Trauma Acute Care Surg.* 2015;79(2):232–237.
36. Scerbo MH, Mumm JP, Gates K, et al. Safety and appropriateness of tourniquets in 105 civilians. *Prehosp Emerg Care.* 2016;20(6):712–722.
37. Harrois A, Libert N, Duranteau J. Acute kidney injury in trauma patients. *Curr Opin Crit Care.* 2017;23(6):447–456.
38. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care.* 2004;8(4):R204–212.
39. Bernier-Jean A, Beaubien-Souligny W, Goupil R, et al. Diagnosis and outcomes of acute kidney injury using surrogate and imputation methods for missing preadmission creatinine values. *BMC Nephrol.* 2017;18(1):141.
40. Kellum JA, Lameire N, Aspelin P, et al. Kidney Disease: Improving Global Outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. *Kidney International Supplements.* 2012;2(1):1–138.
41. Fujii T, Uchino S, Takinami M, Bellomo R. Validation of the kidney disease improving global outcomes criteria for AKI and comparison of three criteria in hospitalized patients. *Clin J Am Soc Nephrol.* 2014;9(5):848–854.
42. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract.* 2012;120(4):c179–184.
43. United States Department of Defense. *Deployment-Limiting Medical Conditions for Service Members and DoD Civilian Employees DoDI 6490.07*. Washington, DC USA: United States Department of Defense; 2010.