

BRIEF REPORT

Full-length plasma skeletal muscle myosin isoform deficiency is associated with coagulopathy in acutely injured patients

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Abstract

Background: Skeletal muscle myosin (SkM) molecules are procoagulant both *in vitro* and *in vivo*. The association of plasma SkM isoforms with blood coagulability and hemostatic capacity has not been defined.

Objectives: We hypothesized that coagulopathy in acutely injured patients is associated with procoagulant plasma SkM heavy chain levels.

Methods: To test this hypothesis, citrated whole blood and plasma from 104 trauma patients were collected and studied to obtain data for rapid thrombelastography, international normalized ratios, and plasma SkM levels. Coagulability parameters were dichotomized by the threshold for the hypercoagulable trauma-induced coagulopathy.

Results: Lower plasma full-length SkM heavy chain (full-SkM) levels were associated with higher international normalized ratio values (>1.3) ($p = .03$). The full-SkM levels were also associated with a lower rate of clot propagation (thrombelastography angle $<65^\circ$) ($p = .004$), and plasma full-SkM levels were positively correlated with the thrombelastography angle ($r^2 = .32$, $p = .0007$). The trauma patient group with the lower plasma full-SkM levels showed an association with lower clot strength (maximum amplitude <55 mm) ($p = .002$), and plasma full-SkM levels positively correlated with maximum amplitude ($r^2 = .27$, $p = .005$). Hyperfibrinolysis was associated with significantly decreased full-SkM levels ($p = .03$). Trauma patients who required red blood cells and fresh frozen plasma transfusions had lower plasma full-SkM levels compared with those without transfusions ($p = .04$ and $.02$, respectively).

Conclusions: In acutely injured trauma patients, lower levels of plasma full-SkM levels are linked to hypocoagulability in trauma-induced coagulopathy, implying that SkM plays a role in the hemostatic capacity in trauma patients and may contribute to trauma-induced coagulopathy.

KEYWORDS

blood coagulation, blood transfusion, myosin, thrombin, trauma

Julia R. Coleman and Hiroshi Deguchi contributed equally to this work and are cofirst authors.

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1 | INTRODUCTION

Thrombin generation is central to the hemostatic balance, and insufficient thrombin generation is linked to bleeding risk.¹ We have previously identified significant association of full-length skeletal muscle myosin (SkM) molecules with hemostatic capacity, specifically with increasing thrombin generation both *in vitro* and *in vivo*.²⁻⁹ SkM is a molecular motor and conventional muscle myosin and is a dimer of heterotrimers, with each trimer containing one heavy chain (HC), one essential light chain, and one regulatory light chain.^{6,10} When the tail of the full length of SkM HC (~240 kDa) (defined as full-SkM) is cleaved, smaller fragments, HMM HC (160 kDa) or S1 HC (95 kDa), are generated. These three SkM HC isoform antigen phenotypes have been identified in human plasma, one of which is associated with isolated pulmonary embolism, suggesting the potential pathological contribution of procoagulant large SkM isoforms to thrombotic disease.¹¹ However, the association of endogenous plasma SkM isoforms with hemostatic capacity has not been explored and defined.

Mechanical trauma disrupts skeletal muscle, and these damaged tissues expose or release SkM to the blood¹²⁻²⁰; this could provide previously unavailable sites for regulation of thrombin generation. Exposed or released SkM's procoagulant actions may contribute to either hemostasis or thrombosis²¹; however, the effect of SkM on coagulation has not been comprehensively examined in trauma patients. Moreover, the mechanisms of trauma-induced coagulopathy have yet to be fully elucidated. A pilot exploratory study suggested that the circulating SkM in human plasma contributes significantly more to the procoagulant potential of trauma patient's plasma than to that of healthy control's plasma.² Therefore, for this study, because SkM appears to have physiological procoagulant functions, we hypothesized that there are associations of plasma SkM isoform levels with blood coagulability in trauma patients.

2 | METHODS

2.1 | Plasma samples from trauma patients

Citrated whole blood and plasmas from 24 healthy controls and 104 adult trauma patients (median age 34 years, 71% male, 66% blunt trauma mechanisms, median new injury severity score [NISS] of 33) were collected at an urban level 1 trauma center (Ernest E Moore Shock Trauma Center at Denver Health Medical Center in Colorado) (Table 1). Because sex and age did not influence SkM isoform levels based on our unpublished data for the healthy control cohort in the Scripps Venous Thrombosis Registry,⁸ we did not analyze to coordinate age- and sex-matched controls. All blood samples were drawn from patients immediately on arrival to the emergency department before any interventions, and plasma was prepared within 2 h. The study was approved by the respective regional institutional review boards and performed under the waiver of consent.

Essentials

- Skeletal muscle myosin (SkM) added to blood exerts procoagulant activity *in vitro*.
- Thrombelastography studies tested relationships of endogenous SkM to trauma blood coagulopathy.
- A SkM heavy chain isoform in trauma patients plasma was correlated with coagulability parameters.
- SkM may contribute to hemostasis in trauma patients and/or to trauma-induced hypocoagulability.

2.2 | Procedures

Citrated rapid thromboelastography (TEG) assay data induced by tissue factor and kaolin using fresh whole blood²²⁻²⁵ and international normalized ratio (INR) data were obtained at the clinical laboratory, in addition to collection of basic demographic, injury-related, and clinical outcome data. Thromboelastography yields the following measurements: activating clotting time (time to clot formation), angle (rate of clot propagation, an effect of fibrinogen), maximum amplitude (MA, clot strength), and LY30 (30 min after MA). Fibrinolytic phenotypes are defined by LY30 and include hyperfibrinolysis, physiologic lysis, and shutdown. Plasma SkM HC isoforms (full-length SkM HC [~240 kDa band, defined as full-SkM], HMM HC [160-kDa band], and S1 HC [95-kDa band]) were detected by immunoblotting¹¹ and were quantified by Li-Cor Odyssey and Li-Cor Image Studio Lite v4.0 software. The relative fluorescence unit values for SkM bands were determined using the standard curve of the dilution of pooled normal plasma subjects (George King Bio-Medical, Inc. Overland Park, KS). Calibration of blots using pooled plasma showed a linear dynamic range of 0.25 to 2 μ l (12.5% to 200% of control plasma). The intra- and interassay coefficient of variations for measuring each band was determined by analyzing the immunoblotting of 22 identical plasma samples on the same gel and on seven different gels for three different levels of each SkM isoform, respectively. The intra-assay coefficients of variability (CV%) for SkM isomers' quantification were <10% for all isomers (9.98%, 8.54%, and 9.68% for full-SkM, SkM-HMM HC, and SkM-S1 HC, respectively), and the interassay CV% values for SkM isomers' quantification of three levels of diluted pooled plasma (50%, 100%, and 200%) were <10% for all isomers (8.53%, 6.97%, and 9.40%, for full-SkM, SkM-HMM HC, and SkM-S1 HC, respectively). These intra- and inter-CV% assay values show that this immunoblotting method reliably quantified the relative amounts of each SkM isoform band.

Control experiments showed that variations in the time between blood collection and plasma preparation of up to 3 h did not influence plasma full-SkM levels because full-SkM levels were not significantly different (\pm 10%) when blood was collected for analysis from four healthy adult controls, and the plasma preparation times were 30, 60, 120, and 180 min after blood collection.

TABLE 1 Description of study population by demographics, injury, physiology, coagulation, and clinical outcomes

Demographics	
Age, y	33.6 (25.5–50.3)
Male sex, n (%)	74 (71%)
Injury characteristics	
Blunt mechanism, n (%)	69 (66%)
NISS	33 (22–43)
GCS	14 (3–15)
TBI, n (%)	45 (43%)
Physiologic markers	
SBP (mm Hg)	102 (82–132)
BD (mEq/L)	7.9 (5.0–12.0)
Lactate (mmol/L)	4.3 (3.1–8.1)
Conventional coagulation assays	
PT/INR	1.1 (1.0–1.5)
PTT, s	29.5 (25.8–40.9)
Initial (field or hospital arrival) TEG measurements	
ACT, s	121 (113–144)
Angle, degrees	69.5 (62.5–74.7)
MA, mm	60.5 (51.5–66.0)
LY30 (%)	1.9 (0.6–8.9)
Outcomes	
Mortality, n (%)	25 (24%)
Transfusion (≥ 1 U RBC) in first 24 h, n (%)	63 (61%)
Units of RBC/first 6 h (among patients who received ≥ 1 U RBC/6 h)	6 (3–10)
Massive transfusion, n (%)	22 (21%)

Note: Continuous variables expressed as median (interquartile range) and proportions expressed as percentages (N). Citrated plasmas from 104 trauma patients collected at an urban level 1 trauma center.

Abbreviations: ACT, activated clotting time; BD, base deficit; GCS, Glasgow Coma Score; LY30, fibrinolysis 30 min after MA; MA, maximum amplitude; NISS, new injury severity score; PT/INR, prothrombin time/international normalized ratio; PTT, partial thromboplastin time; RBC, red blood cell transfusion; SBP, systolic blood pressure; TBI, traumatic brain injury.

3 | RESULT AND DISCUSSION

Overall, whole blood was collected from 104 trauma patients (Table 1), and deidentified plasma samples were analyzed for levels of the plasma SkM heavy chain isoforms by quantitative immunoblotting. The values for various plasma SkM isoform concentrations (full-SkM, SkM-HMM, and SkM-S1) in the trauma group were not statistically different from those of the control group.

Thromboelastography measurements were dichotomized by the optimal transfusion threshold levels that are used to guide hemostatic resuscitation for patients at risk for massive transfusion and considered as hypocoagulable trauma-induced coagulopathy.^{23–25} Among the measured SkM levels, only full-SkM levels showed significant associations with hypocoagulable trauma-induced

coagulopathy based on the following analysis. There were significant differences in full-SkM levels based on multiple TEG measurements. Specifically, patients with an angle of $<65^\circ$ ($n = 27$) had a median full-SkM level of 33.2% versus 117.5% in patients with normal angle $\geq 65^\circ$ ($n = 77$) ($p = .004$) (Table 2). Notably, the angle reflects the speed of fibrin accumulation and polymerization corresponding to the thrombin burst phase.²² Increased level of thrombin activity in whole blood by procoagulant activities of SkM (ie, prothrombinase cofactor and antiheparin/antithrombin activities)^{2–6} may be reflected by the TEG angle measurement. Further, patients with a depressed MA <55 mm ($n = 36$) had a significantly lower median SkM level of 34.0% versus 123.9% in patients with MA ≥ 55 mm ($n = 68$) ($p = .002$) (Table 2). The MA represents clot strength as determined by platelet number and function as well as fibrin cross-linking by factor XIIIa to form a stable clot.²² Because thrombin activates factor XIII and platelets, as well as factor XI, MA could reflect thrombin activities affected by full-SkM plasma level. Further, when TEG measurements were used as continuous values, plasma full-SkM levels positively correlated with the TEG angle ($r^2 = .32$, $p = .0007$) and with MA ($r^2 = .27$, $p = .005$).

In addition to the associations of full-SkM with clot propagation and strength, hyperfibrinolysis (defined by TEG fibrinolysis 30 min after MA [LY30] of $\geq 3.0\%$ ²⁶ and present in 34 patients) was associated with significantly decreased full-SkM levels (median 38.2% vs 104.3% in the 70 patients with physiologic fibrinolysis [LY30 0.9%–2.9%] or fibrinolytic shutdown [LY30 $< 0.9\%$], $p = .03$) (Table 2). This association of the full-SkM deficiency with hyperfibrinolysis may be supported by the fact that SkM was antifibrinolytic in one study because of robust SkM-dependent thrombin generation via activation of thrombin activatable fibrinolysis inhibitor.⁷ This relationship between hyperfibrinolysis and SkM levels is relevant as hyperfibrinolysis has been linked to high levels of mortality in trauma patients.²⁷ Thus, full-SkM deficiency was here associated with not only hypocoagulability but also with hyperfibrinolysis, each of which may induce more bleeding. Further supporting this point, patients who presented with a pathologically elevated INR of >1.3 , considered a hypocoagulable condition,^{28–30} had significantly lower levels of full-SkM (median 76.0% vs 119%, $p = .02$) (Table 2), supporting the association of full-SkM levels with coagulability in TEG, and implying full-SkM contributes to the coagulation system. These data could be further substantiated in future studies using complementary approaches to measure directly thrombin generation (e.g., calibrated automated thrombinography) or coagulation markers (e.g., prothrombin fragment 1+2), which could further define the role of full-SkM affecting thrombin activity.

When the association of plasma full-SkM levels with clinical markers of coagulopathy was examined, trauma patients who required red blood cell and fresh frozen plasma transfusions had lower plasma full-SkM levels compared with the group without blood transfusion ($p = .04$ and $.02$, respectively) (Table 2). These data are consistent with the hypothesis that full-SkM may play a role in the hemostatic capacity in trauma patients, and, when this mechanism is deranged, may contribute to trauma-induced coagulopathy. Plasma

TABLE 2 Association of full-length skeletal muscle myosin (SkM) heavy chain (%) in trauma patients' plasma with coagulation parameters

	Cutoff	N	SkM, % (IQR)	p value
INR	≤1.3	67	119.0 (6.5–183.7)	.03
	>1.3	34	76.0 (0.0–125.3)	
TEG parameter				
ACT, s	≤128	69	104.5 (0.0–148.6)	.13
	>128	35	52.1 (0.0–152.6)	
Angle, degrees	<65	27	33.2 (0.0–92.5)	.004
	≥65	77	117.5 (4.3–177.1)	
MA, mm	<55	36	34.0 (0.0–113.7)	.002
	≥55	68	123.9 (52.0–189.3)	
LY30 (%)	≥3.0	34	38.2 (0–132.1)	.03
	<3.0	70	104.3 (6.5–183.7)	
Blood transfusion				
	Yes or no	N	SkM, % (IQR)	p value
RBC in first 6 h	No	42	107.2 (6.5–194.2)	.04
	Yes	62	82.5 (0.0–132.2)	
FFP in first 6 h	No	42	123.9 (52.2–183.7)	.02
	Yes	62	63.8 (0.0–132.1)	
PLT in first 6 h	No	70	104.5 (0.0–185.3)	.18
	Yes	34	77.3 (0.0–130.9)	
Cryo in first 24 h	No	86	104.2 (0.0–148.8)	.19
	Yes	16	40.7 (0.0–124.6)	

Note: Continuous variables expressed as median values. Citrated plasmas from 104 trauma patients collected at an urban level 1 trauma center. *p* values were obtained by performing Mann-Whitney tests. Cutoff values are defined from the algorithm of US goal-driven approach for a patient at risk of a massive transfusion as the hemostatic resuscitation.²³

Bold values denote statistical significance at the *p* < .05 level.

Abbreviations: ACT, activated clotting time; FFP, fresh frozen plasma transfusion; INR, international normalized ratio; IQR, interquartile range; LY30, fibrinolysis 30 min after MA; MA, maximum amplitude; RBC, red blood cell transfusion; SkM, skeletal muscle myosin; TEG, thrombelastography.

full-SkM-deficient patients had a poorer hemostatic function, leading to more bleeding and required blood transfusion.

Muscle damage (e.g., acute trauma, rhabdomyolysis)^{12–20} increases the total SkM HC antigen levels; however, presently, the metabolic mechanisms regulating plasma SkM levels are not known. In our trauma group, the plasma SkM levels did not differ by injury severity (median 90.9% in patients with NISS <25 [*n* = 9] vs 104.4% in patients with NISS >15 [*n* = 95]), nor as compared with healthy volunteers. However, there were significantly higher levels of SkM found circulating in trauma patients' blood after high-energy penetrating injuries (median 141.3% in penetrating mechanism [*n* = 36] vs 114.6% in blunt mechanism [*n* = 68], *p* = .04). No differences were seen by shock, as defined as systolic blood pressure <90 upon presentation (median 76.6% in shocked patients [*n* = 30] vs 116.6% in nonshocked patients [*n* = 69], *p* = .06). Thus, the injury mechanism was associated with differences in SkM levels; however, more studies are required to characterize the regulatory mechanisms for SkM levels in trauma patients.

The discovery here that the deficiency of full-SkM is associated with hypocoagulable trauma-induced coagulopathy and bleeding relied on newly developed immunoblotting methodology with acceptable intra- and inter-CV% values for plasma SkM. Such immunoblotting methods are not conveniently available in many laboratories,

so the development of easier techniques to quantitate SkM isoform levels (e.g., specific ELISA assays) could extend analyses of SkM isoforms for clinical research.

In conclusion, our findings suggest that, in some trauma patients, full-SkM deficiency is associated with hypocoagulable trauma-induced coagulopathy and hyperfibrinolysis, which leads to more bleeding. Thus, the full-SkM isoform may act as a procoagulant and prohemostatic agent in trauma patients. Therefore, in the setting of acute injury, extensive tissue damage with SkM exposure or release into the bloodstream might enhance plasma full-SkM-induced thrombin generation, thereby contributing to hemostasis. Therefore, the lack of full-SkM, for some reasons (e.g., injury type or consumption at the bleeding site), may cause deficiency of hemostasis. In this scenario, supplemented full-SkM may enhance hemostatic capacity.

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CONFLICTS OF INTEREST

The authors declare no competing financial interests.

AUTHOR CONTRIBUTIONS

Hiroshi Deguchi and John H. Griffin participated in the conception of the study and the overall supervision and integration of all studies. Taichi K. Deguchi and Hiroshi Deguchi were responsible for performing the quantification of plasma SkM. Julia R. Coleman and Ernest E. Moore performed TEG assays. Julia R. Coleman, Mitchel J. Cohen, and Ernest E. Moore were responsible for organizing clinical data and statistical analysis. Hiroshi Deguchi, John H. Griffin, Julia R. Coleman, and Ernest E. Moore analyzed and interpreted the data. Hiroshi Deguchi and John H. Griffin were responsible for writing the manuscript draft, and all authors reviewed and approved the final manuscript.

INFORMED CONSENT

This study was approved by the Colorado Multiple Institutional Review Board (COMIRB 18-0625), and all subjects provided informed consent.

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