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Obesity and Clotting: BMI Independently Contributes to Hypercoagulability after Injury

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Structured Abstract

Background—Though obese patients have high thrombosis rates following injury, the role of obesity in coagulation after trauma remains unknown. We hypothesized that BMI is independently associated with increased measures of hypercoagulability longitudinally after injury.

Methods—Data were prospectively collected for 377 consecutive highest-level trauma activation patients with a body mass index (BMI) ≥ 18.5 kg/m^2. Standard coagulation measures, citrated kaolin and functional fibrinogen thromboelastography (TEG), and clotting factors were measured at 0-120h. BMI categories were defined as *normal weight* (18.5-24.99 kg/m^2), *overweight* (25-29.99 kg/m^2), and *obese* (≥ 30 kg/m^2).

Results—The 377 patients were mostly male (81%) and bluntly injured (61%), with median BMI of 25.8 kg/m^2. 42% were *normal weight* (median BMI 22.5 kg/m^2). There were no differences in age, gender, ISS or base deficit between groups. There were no differences in admission INR/PTT or factors II, V, VII, VIII, X, ATIII, or protein C. However, *obese* patients had higher admission platelet counts (303 vs. 269 × 10^9/L, p=0.004), lower D-dimer (1.88 vs. 4.00 ug/mL, p=0.004), and a trend toward higher factor IX (134 vs. 119 % activity, p=0.042) than *normal weight* patients. Measured by TEG, clot strength (MA) and functional fibrinogen level (FLEV) were also higher on admission for *obese* patients (MA 65.7 vs. 63.4 mm, p=0.016; FLEV 407 vs. 351 mg/dL, p=0.008). In multiple linear regression, the relationship of BMI to clot strength, FLEV, and FIX persisted through 24h. Similarly, the relationship of BMI and platelet count persisted through 120h (all p<0.05). In multiple logistic regression, for every 5kg/m^2 increase in BMI, there was an 85% increase in odds of thromboembolic complication (OR 1.85, CI 1.13-3.08, p=0.017).

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Conflicts of interest: None

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Conclusion—*Obese* trauma patients are hypercoagulable compared to their similarly-injured *normal weight* counterparts, which persists longitudinally after injury. The significance of this hypercoagulability requires elucidation for guidance of anticoagulation in this at-risk group.

Level of Evidence—Level III; prognostic

Keywords

Obesity; coagulation; functional testing; thrombosis; trauma

Background

Trauma remains a public health issue of epidemic proportions. It accounts for the majority of deaths in those 1-44 years old. Early death after injury is primarily attributed to uncontrolled hemorrhage (1-3). Because of this, significant interest exists in understanding the post-injury spectrum of clotting dysfunction that spans from hypocoagulability to hypercoagulability. On presentation, nearly one third of severely injured and bleeding patients have acute traumatic coagulopathy (ATC) portending significant morbidity and a four-fold increase in mortality (4-7). In contrast, ensuing clinical hypercoagulability manifested as venous thromboembolism is seen in up to 60% of patients in the subsequent days following acute injury (8).

Analogous to the trauma epidemic, is the global prevalence of obesity. Obesity is rampant with a yearly mean BMI increase of 0.4-0.5 kg/m^2 worldwide (9). Notably, one-third of adults and nearly one-quarter of children are obese in the United States (10, 11). Paralleling the shocking prevalence of obesity is the ubiquity of obesity-related illnesses including hypertension, heart disease, diabetes, and cancer (12, 13). Perhaps less elucidated, but as pivotal are the proinflammatory and procoagulant consequences of excess adipose tissue conferring up to a 2.5-fold increase in risk of venous and arterial thromboembolism (14-17). The plethora of metabolic sequelae of excess adipose tissue has been intensely investigated in the non-trauma population. Cytokines including interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) contribute to the obesity induced proinflammatory mileau (18-20). Hypercoagulability may be partially due to this chronic low-grade inflammation, but is likely also due to direct effects of adipose tissue on mediators of coagulation.

Recently, much attention has been paid to the clinical role of obesity in morbidity and mortality after trauma (21). Divergent results have added to the debate; in some studies obesity has been found to confer some protection after injury (22, 23), with no effect on mortality (24). Alternatively, other studies have found that obesity is an independent risk factor for complications including thromboembolism and death (25-29). These differing results may reflect an initially protective prothrombotic effect of obesity against early hemorrhagic death, which may later predispose patients to thromboembolic complications contributing to late death and morbidity. Elucidating the interplay of obesity with inflammation and coagulation in the post-injury environment is critical for advancing clinical guidance on prevention of thromboembolism in obese trauma patients.

In order to address the effects of obesity on coagulation after injury, we sought to investigate the influence of obesity on hemostatic function after injury. Functional coagulation testing is beneficial in that it allows for the real time identification of specifics perturbations in clotting (30-33). Thromboelastography (TEG) gives a global assessment in real time of the post-injury clotting profile. From a sample of whole blood, TEG produces a distinctive tracing that measures several parameters representative of clot formation and breakdown in real time. Additionally, the level of functional fibrinogen can be established with functional fibrinogen (FF) TEG. We hypothesized that body mass index (BMI) is independently associated with increased measures of hypercoagulability by TEG longitudinally after injury.

Methods

Demographics, outcomes, and laboratory measures were prospectively collected on arrival and up to 28 days for 377 consecutive highest-level trauma activation patients with a body mass index (BMI) ≥ 18.5 m/kg^2, not anti-coagulated, and without liver failure at a single Level 1 urban trauma center from 2005-2013. Standard coagulation measures (INR, platelet count, von Clauss fibrinogen), citrated kaolin (CK) TEG, FF TEG, and an extensive panel of pro- and anti-coagulant clotting factors were measured at 0, 6, 12, 24, 48, and 120 hours after injury.

Our methodology for sample collection and processing has been previously described (34). In brief, ED samples were collected with placement of a 16G or larger peripheral intravenous line, and subsequent samples were collected via indwelling arterial catheters. Standard laboratory 3.2% (0.109 mol/L) sodium citrate vacuum-sealed tubes were used for all collection. Informed consent was obtained with a waiver of consent for initial blood draws, as approved by the University of California Committee on Human Research. Samples for coagulation factor analysis were centrifuged, and plasma stored at –80°C prior to measurement of fibrinogen, the procoagulant factors II, V, VII, VIII, IX, and X, and the endogenous anticoagulants anti-thrombin III (AT III), protein C, and D-dimer with a Stago Compact Coagulation Analyzer (Diagnostica Stago Inc.; Parsippany, NJ) in accordance with manufacturer instructions. TEG was performed with the TEG 5000 (Haemonetics; Niles, Il) immediately after sample collection. One mL of citrated whole blood was added to a manufacturer-standardized vial containing the clotting activator kaolin and mixed. Following this, 340 uL was transferred from the kaolin vial to the TEG cup, warmed to 37°C, and recalcified with 20 uL of 0.2 mol/L CaCl2. For the FF TEG, 500 uL of citrated blood was added to the FF vial (kaolin + glycoprotein IIb/IIIa antagonist) and mixed; 340 uL was then transferred to the TEG cup, and warmed and recalcified as above. TEG parameters measured included: reaction time (R-time) (time to 2mm of clot formation), K-time (time to 20mm of clot formation), alpha angle (alpha) (the slope of the curve between R-time and K-time measuring the rapidity of fibrin crosslinking), maximum amplitude (MA) (maximum clot strength), the LY30 (percent of lysis at 30 minutes), and FLEV (level of functional fibrinogen). Massive transfusion (MT) was defined as transfusion of 10 units of more of packed red blood cells (pRBC) and fresh frozen plasma (FFP) in first 24 hours. Multi-organ failure (MOF) was defined using the Denver Postinjury Multiple Organ Failure Score (35). Acute respiratory distress syndrome (ARDS) was defined by Berlin definition (36).

Thromboembolic complication included the development of deep venous thrombosis, pulmonary embolism, or cerebrovascular accident at any time after injury. Body mass index (BMI) categories were defined by standard cutoffs: *normal weight* (BMI 18.5-24.99 kg/m^2), *overweight* (BMI 25-29.99 kg/m^2), and *obese* (BMI ≥ 30 kg/m^2).

Data are presented as mean (SD), median (interquartile range), or percentage; univariate comparisons were made using Student's *t* test for normally distributed data, Wilcoxon rank sum or Kruskal Wallis testing for skewed data, and Fisher's exact test for proportions. Multiple univariate comparisons between groups were only judged significant when corrected for multiple comparisons using a standard Bonferroni correction. Multiple linear regression was used at each time point to examine the relationship of BMI with clotting measures. Multiple logistic regression was used to define predictors of the development of thromboembolic complications.

Results

The 377 patients were an injured cohort with a mean ISS of 18 and a mean admission base excess of -3 (Table 1). They were mostly male (81%) with a blunt mechanism of injury (61%; Table 1). 14% required a MT and the mortality at discharge was 12% (Table 1). The median BMI of the cohort was 25.8 kg/m^2, but only 42% were *normal weight* (median BMI 22.5 kg/m^2; Table 2). 32% were *overweight* (median BMI 27.1 kg/m^2), and 26% were *obese* (median BMI 33.0 kg/m^2; Table 2). There were no major differences in baseline patient characteristics including age and gender, and no major differences in overall severity of injury (ISS or base excess), but the *obese* patients had a different injury pattern than their *normal weight* counterparts. They had significantly lower rates of blunt injury and a higher burden of head injury than the *normal weight* patients (blunt injury rate 55% vs. 72%, p=0.007; median head abbreviated injury score (AIS 0 vs. 2, p=0.008; Table 2).

Baseline Measures of Hemostasis

There were no differences in emergency department (ED) plasma-based coagulation measures (international normalized ratio [INR] or partial thromboplastin time [PTT]) across BMI groups. There were also no differences in factor activity levels for factors II, V, VII, VIII, X, ATIII, or protein C across BMI groups (Table 2). However, notably the *obese* patients had significantly higher ED platelet counts (303 vs. 269 × 10^9/L, p=0.004), lower D-dimer levels (1.88 vs. 4.00 ug/mL, p=0.004), and a trend toward higher factor IX activity (134% vs. 119%, p=0.042) than*normal weight* patients. Measured by TEG, there was no difference in clot initiation parameters (R-time, K-time, and alpha; p>0.0167 for multiple comparisons; Table 2). However, *obese* patients had significantly stronger clot strength and higher levels of functioning fibrinogen (MA 65.7 vs. 63.4 mm, p=0.016; FLEV 407 vs. 351 mg/dL, p=0.008; Table 2). Despite the presence of more hemostatic measures of clotting in the *obese* compare to the *normal weight* patients, there were no notable univariate differences in transfusion of pRBC, FFP, or platelet apheresis (PLTs) units (all p>0.0167 for multiple comparisons; Table 2). Similarly, there were also no univariate differences in MT, length of stay, or complications including ARDS, MOF, or mortality rates (all p>0.0167 for multiple comparisons; Table 2). However, there was a trend toward higher rates of

thromboembolic complications in *obese* compared to *normal weight* patients (9% vs. 4%, p=0.1810; Table 2).

Longitudinal Measures of Hemostasis

Given the *obese* patients demonstrated more hemostatic measures of clotting on admission, we then performed multiple linear regression (controlling for age, injury severity, gender, and all products received up to each timepoint) at serial timepoints after injury (6, 12, 24, 48, and 120 hours) to examine the independent relationship of BMI to functional clotting parameters, factor levels, and INR over time. There were no statistically significant independent relationships or notable trends between BMI and clot initiation parameters (R-time, K-time, alpha angle) or functional measures of fibrinolysis (LY30) at any timepoint after injury (all p>0.05 at all timepoints). Similarly, there were no statistically significant independent relationships or notable trends between BMI and factor levels for the procoagulant factors II, V, VII, VIII, X, protein C, ATIII, or INR at any timepoint after injury (all p>0.05 at all timepoints). However, there was a significant independent increase in Factor IX activity for each 5 kg/m^2 increase in BMI at 0, 6, and 12, 48, and 120 hours after injury (Table 3). This relationship was not present at 24 hours (Table 3).

Similarly, there was a significant independent increase in clot strength (MA) for each 5 kg/m^2 increase in BMI at 0, 6, 12, and 24 hours after injury (all p<0.*05;* Table 3). However, this relationship of BMI to clot strength was not present past 24 hours. Paralleling overall clot strength, BMI and functional fibrinogen levels (FLEV) were positively associated through 24 hours (Table 4), but not beyond. Perhaps the most notable relationship was the significant increase in platelet count with increasing BMI at all timepoints after injury (Table 4). This peaked at 12 hours, where for each $5kg/m^2$ increase in BMI the platelet count increased by $33 \times 10^{9/L}$ (p<0.001; Table 4). Lastly, confirming the lower admission D-dimer in the *obese* group seen in our univariate comparison, we found that D-dimer independently decreased with increasing BMI out to 12 hours (Table 5).

Thromboembolic Complications

Finally, we sought to examine whether the increased factor IX activity, increased overall clot strength, increased functioning levels of fibrinogen, increased platelet count, and decreased fibrinolysis seen longitudinally after injury corresponded with an increased risk of developing a thromboembolic complication. In a multiple logistic regression controlling for injury severity, transfusion, and deep venous thromboembolism (DVT) prophylaxis, we found that for every $5kg/m^2$ increase in BMI, there was an 85% increase in odds of developing a thromboembolic complication (OR 1.85, CI 1.12-3.08, p=0.017; Table 6).

Discussion

With the growing prevalence of obesity coupled with the increased incidence of injury worldwide, elucidating the intimate associations and relationships between these two disease states is critical. Only 42% of our severely injured cohort was *normal weight*, which highlights that the majority of injured patients suffer from the effects of excess adipose tissue. This excess adipose is far from inert and plays a cardinal role in the biologic and

physiologic milieu seen with obesity. Untangling its complex interaction with inflammation and coagulation will help contribute to a better understanding of the clinical outcome differences seen in obese patients after injury and may help with targeted treatment of this at-risk group. We found that following injury, *obese* patients are hypercoagulable compared to their similarly injured *normal weight* counterparts. This hypercoagulability persists after injury as demonstrated by increased FIX activity, increased levels of functioning fibrinogen, relative thrombocytosis, stronger clot, and decreased evidence of clot lysis with increasing BMI. The importance of these relationships is highlighted by an independent 85% increased odds of developing a thromboembolic complication after injury for each 5kg/m^2 increase in BMI.

Our cohort of *obese* patients had lower rates of blunt injury and head injury, which corresponds to prior studies demonstrating some potential protective aspects of overall adipose volume to injury patterns (22, 23). However, there was no difference in overall injury severity or mortality rates between *obese* and *normal weight* patients (24). Despite this, the *obese* patients had higher rates of thromboembolic complications and BMI was a significant independent predictor of development of thromboembolic complications even when controlling for injury severity, product transfusion, and DVT prophylaxis.

Obesity induced chronic low-grade inflammation may be partially responsible for this increased rate of thromboembolic complications. However, adipose-specific mediation of coagulation may play a pivotal role in thrombotic potential following injury. Specific pathways that have been investigated include increased thrombin generation due to excess release of and tissue factor from adipose cells (20, 37), thrombogenic modulation of platelet aggregation induced by leptin and adiponectin (15, 20, 38), and decreased fibrinolysis due to excess release of plasminogen activator inhibitor-1 (PAI-1) from adipose cells (39). Additionally, there is speculation that enhanced biosynthesis of coagulation factors including fibrinogen may be due to obesity-induced alterations in liver metabolism. The acute phase hepatic production of fibrinogen may be related to the IL-6 mediated inflammatory state (19, 20). Kaye *et al* recently studied coagulation in obesity discordant monozygotic twin pairs and found higher activities of fibrinogen, factor IX, XI, XII, and PAI-1 in the obese twins compared to their lean monozygotic pair (40).

Supportive of these pathways, we found that immediately following injury our study's *obese* patients were relatively hypercoagulable compared to their *normal weight* counterparts. A balance between clot formation and breakdown determines ultimate clotting potential, and our study demonstrated that *obese* injured patients exhibited both stronger clot and less fibrinolysis. The stronger clot is presumably due to the significant increases in both of the primary contributors to clot strength: fibrin and platelets. This is evident in our study because the *obese* patients had significantly higher levels of functioning fibrinogen as well as a significant relative thrombocytosis compared to their *normal weight* counterparts. Although there was no statistically significant difference in fibrinolysis by TEG between the groups, there was a stepwise trend with the lowest amount of fibrinolysis in the *obese* patients. This corresponds with the finding of a significantly lower D-dimer in the *obese* patients compared to their *normal weight* counterparts. Interestingly, there was no difference in the functional measure of fibrinolysis. However, Raza et al recently demonstrated that

functional measures of fibrinolysis are not as sensitive in detection as plasmin-antiplasmin complex levels or D-dimer levels (41).

The hypercoagulability found immediately following injury in the *obese* patients persisted to at least 24 hours. The BMI dependent increase in factor IX activity and the relative thrombocytosis persisted out to 5 days after injury independent of injury severity or transfusion of pRBC, FFP, or PLTs. However, we found that the BMI dependent increase in clot strength and functional levels of fibrinogen only persisted to 24 hours after injury, and the decrease in fibrinolysis measured by D-dimer only persisted to 12 hours after injury. This increase in clot strength and decreased clot breakdown needs further study, but it appears that several independent relationships between BMI and several mediators of coagulation may contribute to the ultimate increased risk of thromboembolism. It may be that the relationship between fibrinogen function and BMI disappears past 24 hours due to the initiation of heparin based DVT prophylaxis, which does not have any effect on the relative thrombocytosis seen out to 5 days. Unfortunately, we cannot examine this due to our lack of data on the timing of initiation of DVT prophylaxis. Alternatively, it may be that the overwhelming propensity of injury-induced hypercoagulability leads to increasing fibrinogen function in all severely injured patients overcoming the independent effect of BMI past 24 hours. These complex relationships need to be further examined.

We recognize several limitations of our study including the prospective observational nature. We do not know the timing or dosages of DVT prophylaxis in order to adjust for its contribution to the effect of BMI on the functional level of fibrinogen. Additionally, there is no standardized heparin based DVT prophylaxis or standardized algorithm at our institution. Akin to this, we do not perform routine screening for DVT, and therefore only report clinically significant thromboembolic complications. There may be a much higher incidence of non-clinically significant thromboembolism in this population. However, even with a potential underestimate of the true incidence, we found a significant independent association of BMI and thromboembolism.

In examining the independent association of BMI and the mediators of coagulation past 24 hours, the later regression timepoints have fewer patients due to death and discharge. This could cause a type II error and may be a potential explanation for the lack of associations seen between functional fibrinogen level and D-dimer past 24 hours. Lastly, we cannot define any directly causal pathways between increased factor IX activity, increased levels of functional fibrinogen, increased platelet counts, stronger clot, and decreased D-dimer leading to the increased risk of thromboembolism in the *obese* patients. However the association of BMI with these mediators of hemostasis is supported by previous basic science and cellular investigations of adipose-induced coagulation effects. Future clinical studies with matching uninjured obese patients and animal models of genetically identical obesity discordant subjects will be critical to further elucidate the interplay of obesity, inflammation, and injury.

In conclusion, following injury *obese* patients are hypercoagulable compared to their similarly injured *normal weight* counterparts, which persists to at least 24 hours after injury. Additionally, BMI is independently associated with an 85% increased risk of developing a

thromboembolic complication after injury. These findings are critical and need to be further investigated to guide management of anticoagulation in this at-risk group.

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References

1. Norton R, Kobusingye O. Injuries. The New England journal of medicine. 2013; 368(18):1723–30. Epub 2013/05/03. [PubMed: 23635052]
2. Injury: The Leading Cause of Death Among Persons 1-44. 2013. [cited 2013 March 31]; Available from: http://www.cdc.gov/injury/overview/leading_cod.html
3. Teixeira PG, Inaba K, Hadjizacharia P, Brown C, Salim A, Rhee P, Browder T, Noguchi TT, Demetriades D. Preventable or potentially preventable mortality at a mature trauma center. The Journal of trauma. 2007; 63(6):1338–46. discussion 46-7. Epub 2008/01/24. [PubMed: 18212658]
4. MacLeod JB, Lynn M, McKenney MG, Cohn SM, Murtha M. Early coagulopathy predicts mortality in trauma. The Journal of trauma. 2003; 55(1):39–44. Epub 2003/07/12. [PubMed: 12855879]
5. Cohen MJ, Call M, Nelson M, Calfee CS, Esmon CT, Brohi K, Pittet JF. Critical role of activated protein C in early coagulopathy and later organ failure, infection and death in trauma patients. Annals of surgery. 2012; 255(2):379–85. Epub 2011/12/03. [PubMed: 22133894]
6. Cohen MJ, West M. Acute traumatic coagulopathy: from endogenous acute coagulopathy to systemic acquired coagulopathy and back. The Journal of trauma. 2011; 70(5 Suppl):S47–9. Epub 2011/08/24. [PubMed: 21841573]
7. Kutcher ME, Kornblith LZ, Vilardi RF, Redick BJ, Nelson MF, Cohen MJ. The Natural History and Effect of Resuscitation Ratio on Coagulation After Trauma: A Prospective Cohort Study. Annals of surgery. 2014 Epub 2014/05/23.
8. Geerts WH, Code KI, Jay RM, Chen E, Szalai JP. A prospective study of venous thromboembolism after major trauma. The New England journal of medicine. 1994; 331(24):1601–6. Epub 1994/12/15. [PubMed: 7969340]
9. Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ, Singh GM, Gutierrez HR, Lu Y, Bahalim AN, et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. Lancet. 2011; 377(9765):557–67. Epub 2011/02/08. [PubMed: 21295846]
10. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. JAMA : the journal of the American Medical Association. 2014; 311(8):806–14. Epub 2014/02/27.
11. Malik VS, Willett WC, Hu FB. Global obesity: trends, risk factors and policy implications. Nature reviews Endocrinology. 2013; 9(1):13–27. Epub 2012/11/21.
12. Sjostrom L, Larsson B, Backman L, Bengtsson C, Bouchard C, Dahlgren S, Hallgren P, Jonsson E, Karlsson J, Lapidus L, et al. Swedish obese subjects (SOS). Recruitment for an intervention study and a selected description of the obese state. International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity. 1992; 16(6):465–79. Epub 1992/06/01.
13. Sjostrom L. Review of the key results from the Swedish Obese Subjects (SOS) trial - a prospective controlled intervention study of bariatric surgery. Journal of internal medicine. 2013; 273(3):219–34. Epub 2012/11/21. [PubMed: 23163728]
14. Bray GA. Medical consequences of obesity. The Journal of clinical endocrinology and metabolism. 2004; 89(6):2583–9. Epub 2004/06/08. [PubMed: 15181027]
15. Samad F, Ruf W. Inflammation, obesity, and thrombosis. Blood. 2013; 122(20):3415–22. Epub 2013/10/05. [PubMed: 24092932]

16. Stein PD, Beemath A, Olson RE. Obesity as a risk factor in venous thromboembolism. The American journal of medicine. 2005; 118(9):978–80. Epub 2005/09/17. [PubMed: 16164883]
17. Eichinger S, Hron G, Bialonczyk C, Hirschl M, Minar E, Wagner O, Heinze G, Kyrle PA. Overweight, obesity, and the risk of recurrent venous thromboembolism. Archives of internal medicine. 2008; 168(15):1678–83. Epub 2008/08/13. [PubMed: 18695082]
18. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. The Journal of clinical investigation. 2006; 116(7):1793–801. Epub 2006/07/11. [PubMed: 16823477]
19. Fontana L, Eagon JC, Trujillo ME, Scherer PE, Klein S. Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. Diabetes. 2007; 56(4):1010–3. Epub 2007/02/09. [PubMed: 17287468]
20. Faber DR, de Groot PG, Visseren FL. Role of adipose tissue in haemostasis, coagulation and fibrinolysis. Obesity reviews : an official journal of the International Association for the Study of Obesity. 2009; 10(5):554–63. Epub 2009/05/23. [PubMed: 19460118]
21. Winfield RD, Bochicchio GV. The critically injured obese patient: a review and a look ahead. Journal of the American College of Surgeons. 2013; 216(6):1193–206. Epub 2013/03/26. [PubMed: 23522437]
22. Desapriya E, Giulia S, Subzwari S, Peiris DC, Turcotte K, Pike I, Sasges D, Hewapathirane DS. Does Obesity Increase the Risk of Injury or Mortality in Motor Vehicle Crashes? A Systematic Review and Meta-Analysis. Asia-Pacific journal of public health / Asia-Pacific Academic Consortium for Public Health. 2011 Epub 2011/12/22.
23. Osborne Z, Rowitz B, Moore H, Oliphant U, Butler J, Olson M, Aucar J. Obesity in trauma: outcomes and disposition trends. American journal of surgery. 2014; 207(3):387–92. discussion 91-2. Epub 2014/03/04. [PubMed: 24581763]
24. Newell MA, Bard MR, Goettler CE, Toschlog EA, Schenarts PJ, Sagraves SG, Holbert D, Pories WJ, Rotondo MF. Body mass index and outcomes in critically injured blunt trauma patients: weighing the impact. Journal of the American College of Surgeons. 2007; 204(5):1056–61. discussion 62-4. Epub 2007/05/08. [PubMed: 17481540]
25. Ditillo M, Pandit V, Rhee P, Aziz H, Hadeed S, Bhattacharya B, Friese RS, Davis K, Joseph B. Morbid obesity predisposes trauma patients to worse outcomes: a National Trauma Data Bank analysis. The journal of trauma and acute care surgery. 2014; 76(1):176–9. Epub 2013/12/26. [PubMed: 24368375]
26. Glance LG, Li Y, Osler TM, Mukamel DB, Dick AW. Impact of obesity on mortality and complications in trauma patients. Annals of surgery. 2014; 259(3):576–81. Epub 2013/11/23. [PubMed: 24263314]
27. Andruszkow H, Veh J, Mommsen P, Zeckey C, Hildebrand F, Frink M. Impact of the body mass on complications and outcome in multiple trauma patients: what does the weight weigh? Mediators of inflammation. 2013; 2013:345702. Epub 2013/09/12. [PubMed: 24023413]
28. Byrnes MC, McDaniel MD, Moore MB, Helmer SD, Smith RS. The effect of obesity on outcomes among injured patients. The Journal of trauma. 2005; 58(2):232–7. Epub 2005/02/12. [PubMed: 15706181]
29. Brown CV, Neville AL, Rhee P, Salim A, Velmahos GC, Demetriades D. The impact of obesity on the outcomes of 1,153 critically injured blunt trauma patients. The Journal of trauma. 2005; 59(5): 1048–51. discussion 51. Epub 2005/12/31. [PubMed: 16385276]
30. Kheirabadi BS, Crissey JM, Deguzman R, Holcomb JB. In vivo bleeding time and in vitro thrombelastography measurements are better indicators of dilutional hypothermic coagulopathy than prothrombin time. The Journal of trauma. 2007; 62(6):1352–9. discussion 9-61. Epub 2007/06/15. [PubMed: 17563647]
31. Martini WZ, Cortez DS, Dubick MA, Park MS, Holcomb JB. Thrombelastography is better than PT, aPTT, and activated clotting time in detecting clinically relevant clotting abnormalities after hypothermia, hemorrhagic shock and resuscitation in pigs. The Journal of trauma. 2008; 65(3): 535–43. Epub 2008/09/12. [PubMed: 18784565]
32. Park MS, Martini WZ, Dubick MA, Salinas J, Butenas S, Kheirabadi BS, Pusateri AE, Vos JA, Guymon CH, Wolf SE, et al. Thromboelastography as a better indicator of hypercoagulable state

after injury than prothrombin time or activated partial thromboplastin time. The Journal of trauma. 2009; 67(2):266–75. discussion 75-6. Epub 2009/08/12. [PubMed: 19667878]

33. Holcomb JB, Minei KM, Scerbo ML, Radwan ZA, Wade CE, Kozar RA, Gill BS, Albarado R, McNutt MK, Khan S, et al. Admission rapid thrombelastography can replace conventional coagulation tests in the emergency department: experience with 1974 consecutive trauma patients. Annals of surgery. 2012; 256(3):476–86. Epub 2012/08/08. [PubMed: 22868371]
34. Kornblith LZ, Kutcher ME, Redick BJ, Calfee CS, Vilardi RF, Cohen MJ. Fibrinogen and platelet contributions to clot formation: implications for trauma resuscitation and thromboprophylaxis. The journal of trauma and acute care surgery. 2014; 76(2):255–6. discussion 62-3. Epub 2014/01/25. [PubMed: 24458031]
35. Moore FA, Sauaia A, Moore EE, Haenel JB, Burch JM, Lezotte DC. Postinjury multiple organ failure: a bimodal phenomenon. The Journal of trauma. 1996; 40(4):501–10. discussion 10-2. Epub 1996/04/01. [PubMed: 8614027]
36. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS. Acute respiratory distress syndrome: the Berlin Definition. JAMA : the journal of the American Medical Association. 2012; 307(23):2526–33. Epub 2012/07/17.
37. Samad F, Pandey M, Loskutoff DJ. Tissue factor gene expression in the adipose tissues of obese mice. Proceedings of the National Academy of Sciences of the United States of America. 1998; 95(13):7591–6. Epub 1998/06/24. [PubMed: 9636194]
38. Riba R, Hughes CE, Graham A, Watson SP, Naseem KM. Globular adiponectin induces platelet activation through the collagen receptor GPVI-Fc receptor gamma chain complex. Journal of thrombosis and haemostasis : JTH. 2008; 6(6):1012–20. Epub 2008/04/19. [PubMed: 18419742]
39. Simpson AJ, Booth NA, Moore NR, Bennett B. Distribution of plasminogen activator inhibitor (PAI-1) in tissues. Journal of clinical pathology. 1991; 44(2):139–43. Epub 1991/02/01. [PubMed: 1864986]
40. Kaye SM, Pietilainen KH, Kotronen A, Joutsi-Korhonen L, Kaprio J, Yki-Jarvinen H, Silveira A, Hamsten A, Lassila R, Rissanen A. Obesity-related derangements of coagulation and fibrinolysis: a study of obesity-discordant monozygotic twin pairs. Obesity (Silver Spring). 2012; 20(1):88–94. Epub 2011/10/01. [PubMed: 21959347]
41. Raza I, Davenport R, Rourke C, Platton S, Manson J, Spoors C, Khan S, De'Ath HD, Allard S, Hart DP, et al. The incidence and magnitude of fibrinolytic activation in trauma patients. Journal of thrombosis and haemostasis : JTH. 2013; 11(2):307–14. Epub 2012/11/28. [PubMed: 23176206]

Table 1

Demographics and outcomes

	N=377
Age (years)	33 (24-49)
Male gender	81%
BMI (kg/m2)	25.8 (22.9-30.1)
Blunt injury rate	61%
ISS	18 +/- 15
ED arrival GCS	14 (7-15)
AIS-head	0 (0-4)
Prehospital crystalloid (mL)	100 (0-250)
ED admit temperature (°)	36.2 +/- 0.9
Admit pH	7.31 +/- 0.12
Admit base excess	-3 +/- 6
Admit INR	1.1 (1-1.2)
Admit PTT (s)	28 (26-31)
Admit platelet count (x 10^9/L)	274 (225-332)
Admit fibrinogen (mg/dL)	228 +/- 96
Admit Factor II (% activity)	75 +/- 21
Admit Factor V (% activity)	40 (24-57)
Admit Factor VII (% activity)	82 (62-107)
Admit Factor VIII (% activity)	167 (85-266)
Admit Factor IX (% activity)	123 +/- 44
Admit Factor × (% activity)	78 +/- 22
Admit ATIII (% activity)	74 +/- 27
Admit protein C (% activity)	82 +/- 28
Admit D-dimer (ug/mL)	3.34 (0.58-6.77)
Admit CK R-time (min)	4.6 +/- 1.4
Admit CK K-time (min)	1.3 (1.2-1.7)
Admit CK alpha angle (°)	69.3 +/- 6.1
Admit CK MA (mm)	64.4 +/- 5.8
Admit CK LY30 (%)	0.8 (0.1-2.7)
Admit FLEV (mg/dL)	368 +/- 90
pRBC 0-24 hours (units)	0 (0-3)
FFP 0-24 hours (units)	0 (0-2)
PLTS 0-24 hours (units)	0 (0-0)
MT in 24 hours	14%
Total hospital days	6 (3-17)
Ventilator free days	2 (0-6)
VAP rate	1%
ARDS rate	11%
MOF rate	9%

Mortality rate at 6 hours	1%
Mortality rate at 24 hours	3%
Mortality rate at discharge	12%
TE complication rate	6%

* Patient demographics for the 377 patients. Data are mean +/- SD, median (inter-quartile range), or n (%) as indicated. Data for skewed variables reported as median with inter-quartile ranges. BMI=body mass index. ED=emergency department. GCS=Glascow Coma Scale. ISS=injury severity score. AIS=abbreviated injury score. INR=international normalized ratio. PTT=partial thromboplastic time. ATIII=antithrombin III. CK=citrated kaolin. R-time=reaction time. MA=maximum amplitude. LY30=lysis at 30 min. FLEV=functional fibrinogen level. pRBC=packed red blood cell units. FFP=fresh frozen plasma units. PLTS=platelet units. MT=massive transfusion. Ventilator free days, counted for the first 28 days of hospitalization. Patients who expired received 0 ventilator free days. VAP=ventilator associated pneumonia. ARDS=acute respiratory distress syndrome by Berlin criteria. MOF=multiple organ failure. TE=thromboembolic

Table 2

Demographics and outcomes by BMI category (*normal weight, overweight, obese/superobese*)

	Normal weight N=160 (42%)	*Overweight* N=120 (32%)	*Obese* N=97 (26%)	*p*-value	*p*-value (*normal weight* vs *obese)*
Age (years)	34 (24-51)	33 (26-47)	33 (24-45)	0.6642	0.3493
Male gender	78%	85%	84%	0.2380	0.2660
BMI (kg/m2)	22.5 (20.9-23.8)	27.1 (25.9-28.3)	33.0 (31.3-36.1)	**0.0001**	**0.0001**
Blunt injury rate	72%	51%	55%	**0.0010**	**0.0070**
ISS	18 +/- 15	18 +/- 15	17 +/- 15	0.6313	0.3022
ED arrival GCS	13 (7-15)	14 (8-15)	14 (7-15)	0.1480	0.1514
AIS-head	2 (0-4.5)	0 (0-3.5)	0 (0-3)	**0.0129**	**0.0083**
Prehospital crystalloid (mL)	50 (0-250)	100 (0-250)	100 (0-250)	0.4915	0.4282
ED admit temperature (°)	36.1 +/- 0.9	36.2 +/- 0.9	36.3 +/- 1.0	0.6560	0.3774
Admit pH	7.31 +/- 0.12	7.31 +/- 0.11	7.29 +/- 0.15	0.3640	0.2349
Admit base excess	-2.4 +/- 5.5	-3.2 +/- 4.6	-3.7 +/- 6.5	0.2872	0.1494
Admit INR	1.1 (1.1-1.2)	1.1 (1-1.2)	1.1 (1-1.2)	0.3063	0.2687
Admit PTT (s)	28 (26-32)	28 (26-31)	28 (26-30)	0.4731	0.2448
Admit platelet count (× 109/L)	269+/- 83	283 +/- 80	303 +/- 101	**0.0105**	**0.0038**
Admit fibrinogen (mg/dL)	230 +/- 94	210 +/- 100	243 +/- 95	0.2050	0.4233
Admit Factor II (% activity)	76 +/- 18	72 +/- 25	77 +/- 23	0.4983	0.8298
Admit Factor V (% activity)	39 (23-58)	41 (19-53)	41 (28-61)	0.3127	0.4349
Admit Factor VII (% activity)	82 (63-107)	79 (55-100)	77 (62-111)	0.4481	0.6201
Admit Factor VIII (% activity)	156 (89-268)	176 (108-298)	147 (74-263)	0.5145	0.7304
Admit Factor IX (% activity)	119 +/- 39	118 +/- 46	134 +/- 48	0.0942	0.0416
Admit Factor × (% activity)	78 +/- 18	75 +/- 26	81 +/- 24	0.3473	0.3694
Admit ATIII (% activity)	79 +/- 26	68 +/- 24	72 +/- 30	0.0711	0.3573
Admit protein C (% activity)	79 +/- 27	84 +/- 26	84 +/- 31	0.5522	0.1289
Admit D-dimer (ug/mL)	4.00 (1.13-7.70)	2.67 (0.44-6.29)	1.88 (0.45-4.00)	**0.0128**	**0.0039**
Admit CK R-time (min)	4.4 +/- 1.4	4.6 +/- 1.5	4.7 +/- 1.3	0.2835	0.1036
Admit CK K-time (min)	1.3 (1.2-1.6)	1.4 (1.2-1.8)	1.3 (1.2-1.7)	0.8687	0.8955
Admit CK alpha angle (°)	69.3 +/- 6.4	69.2 +/- 5.9	69.4 +/- 6.1	0.7850	0.8857
Admit CK MA (mm)	63.4 +/- 6.1	64.5 +/- 5.0	65.7 +/- 6.1	0.0374	**0.0157**

	Normal weight N=160 (42%)	*Overweight* N=120 (32%)	*Obese* N=97 (26%)	*p*-value	*p*-value (*normal weight* vs *obese*)
Admit CK LY30 (%)	1.0 (0.1-2.5)	0.9 (0.1-2.8)	0.6 (0.1-2.7)	0.9524	0.9456
Admit FLEV (mg/dL)	351 +/- 84	358 +/- 70	407 +/- 105	0.0670	**0.0077**
pRBC 0-24 hours (units)	0 (0-2.5)	0 (0-3.5)	0 (0-2)	0.6480	0.7743
FFP 0-24 hours (units)	0 (0-1)	0 (0-2)	0 (0-1)	0.1300	0.9672
PLTS 0-24 hours (units)	0 (0-0)	0 (0-0)	0 (0-0)	0.6655	0.5200
MT in 24 hours	12%	18%	5%	0.2870	0.5270
Total hospital days	7 (3-15)	7 (2-20)	6 (3-18)	0.7482	0.4431
Ventilator free days	26 (21-28)	27 (19-28)	27 (20-28)	0.8412	0.6154
VAP rate	0%	2%	0%	0.1620	n/d
ARDS rate	12%	12%	8%	0.7330	0.2880
MOF rate	9%	8%	9%	0.9730	1.0000
Mortality rate at 6 hours	1%	1%	0%	0.7900	0.5280
Mortality rate at 24 hours	2%	3%	3%	0.7160	0.6760
Mortality rate at discharge	15%	9%	10%	0.3080	0.3440
TE complication rate	4%	4%	9%	0.2410	0.1810

* Comparisons of the *normal weight*, *overweight*, and *obese* groups. Data are mean +/- SD, median (inter-quartile range), or n (%) as indicated. Data for skewed variables reported as median with inter-quartile ranges. *p*-value bolded if <0.0167 as corrected for multiple comparisons. BMI=body mass index. ED=emergency department. GCS=Glascow Coma Scale. ISS=injury severity score. AIS=abbreviated injury score. INR=international normalized ratio. PTT=partial thromboplastic time. ATIII=antithrombin III. CK=citrated kaolin. R-time=reaction time. MA=maximum amplitude. LY30=lysis at 30 min. FLEV=functional fibrinogen level. pRBC=packed red blood cell units. FFP=fresh frozen plasma units. PLTS=platelet units. MT=massive transfusion. Ventilator free days, counted for the first 28 days of hospitalization. Patients who expired received 0 ventilator free days. VAP=ventilator associated pneumonia. ARDS=acute respiratory distress syndrome by Berlin criteria. MOF=multiple organ failure. TE=thromboembolic

Table 3

Independent relationship of BMI with factor IX and clot strength at serial timepoints after injury

Independent relationship of BMI and factor IX activity at serial timepoints after injury

	Factor IX (% activity) per 5 kg/m^2 increase in BMI	CI			*p*-value
0h	7.79	1.51	-	14.06	**0.015**
6h	13.88	4.80	-	22.95	**0.003**
12h	9.30	1.74	-	16.87	**0.016**
24h	7.83	-2.44	-	18.10	0.133
48h	15.71	3.93	-	27.50	**0.010**
120h	28.21	3.47	-	52.93	**0.027**

Covariates at each timepoint: age, injury severity, gender, and all products (pRBC, FFP, PLTs) received up to that timepoint. *P*-value bolded for <0.05.

Independent relationship of BMI and clot strength (MA) at serial timepoints after injury

	CK MA change (mm) per 5 kg/m^2 increase in BMI	CI			*p*-value
0h	1.01	0.39	-	1.62	**0.002**
6h	1.24	0.39	-	2.07	**0.004**
12h	1.17	0.36	-	1.97	**0.005**
24h	0.95	0.08	-	1.82	**0.032**
48h	0.35	-0.57	-	1.27	0.455
120h	0.63	-1.03	-	2.28	0.449

Covariates at each timepoint: age, injury severity, gender, and all products (pRBC, FFP, PLTs) received up to that timepoint. *P*-value bolded for <0.05. CK MA= citrated kaolin TEG maximum amplitude (mm).

Table 4

Independent relationship of BMI with functional fibrinogen level and platelet count at serial timepoints after injury

Independent relationship of BMI and functional fibrinogen level (FLEV) at serial timepoints after injury

	FLEV change (ng/mL) per 5 kg/m^2 increase in BMI	CI			*p*-value
0h	23.20	10.31	-	36.10	**0.001**
6h	19.92	0.29	-	39.55	**0.047**
12h	19.85	3.84	-	35.87	**0.016**
24h	15.96	0.04	-	31.88	**0.049**
48h	-8.70	-38.14	-	20.73	0.545
120h	-5.20	-55.84	-	45.46	0.828

Covariates at each timepoint: age, injury severity, gender, and all products (pRBC, FFP, PLTs) received up to that timepoint. *P*-value bolded for <0.05. CK MA= citrated kaolin TEG maximum amplitude (mm).

Independent relationship of BMI and platelet count at serial timepoints after injury

	Platelet count (× 10$^{9/L}$) per 5 kg/m^2 increase in BMI	CI			*p*-value
0h	10.94	2.32	-	19.56	**0.013**
6h	23.30	3.79	-	42.81	**0.020**
12h	33.33	16.60	-	50.07	**<0.001**
24h	10.57	3.77	-	17.38	**0.002**
48h	11.57	4.86	-	18.28	**0.001**
120h	12.54	0.49	-	24.59	**0.041**

Covariates at each timepoint: age, injury severity, gender, and all products (pRBC, FFP, PLTs) received up to that timepoint. *P*-value bolded for <0.05.

Table 5

Independent relationship of BMI with D-dimer at serial timepoints after injury

Independent relationship of BMI and D-dimer at serial timepoints after injury					
	Ddimer (ug/mL) per 5 kg/m^2 increase in BMI			**CI**	***p*-value**
0h	-1.09	-1.65	-	-0.52	**<0.001**
6h	-0.56	-1.00	-	-0.12	**0.014**
12h	-0.41	-0.85	-	0.04	**0.073**
24h	-0.28	-0.78	-	0.21	0.253
48h	-9.58	-0.65	-	7.25	0.260
120h	0.21	-0.66	-	1.08	0.629

Covariates at each timepoint: age, injury severity, gender, and all products (pRBC, FFP, PLTs) received up to that timepoint. *P*-value bolded for <0.05.

Table 6

Multivariate predictors of thromboembolic complications

	Univariate	CI			p	Multivariate	CI			p
Age (years)	1.02	0.99	-	1.04	0.195					
Male gender	0.55	0.20	-	1.47	0.231					
BMI (5kg/m^2)	1.07	1.00	-	1.15	0.053	**1.85**	**1.12**	-	**3.08**	**0.017**
ISS	1.03	1.01	-	1.06	0.018	0.98	0.93	-	1.03	0.403
DVT prophylaxis given in 1st 5 days	4.46	1.51	-	13.22	0.007	4.99	0.99	-	25.10	0.051
Total product (units) from 0-72 hours	1.04	1.02	-	1.06	<0.001	**1.06**	**1.01**	-	**1.11**	**0.016**

*n=377. Bolded: $p<0.05$ for multivariate predictors. AUC=0.83. ISS=injury severity score. DVT=deep venous thromboembolism. Total product= number of units of packed red blood cells, fresh frozen plasma, and platelets