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Nilsson, Abraham

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BioFACTS: biomarkers of rhabdomyolysis in the diagnosis of acute compartment syndrome – protocol for a prospective multinational, multicentre study involving patients with tibial fractures

Abraham Nilsson ,[1] Thomas Ibounig ,[2] Johan Lyth,[3] Björn Alkner,[4] Ferdinand von Walden ,[5] Lotta Fornander,[6] Lasse Rämö ,[2] Andrew Schmidt,[7] Jörg Schilcher [1]

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For numbered affiliations see end of article.

Correspondence to
Dr Jörg Schilcher;
jorg.schilcher@liu.se

ABSTRACT

Introduction The ischaemic pain of acute compartment syndrome (ACS) can be difficult to discriminate from the pain linked to an associated fracture. Lacking objective measures, the decision to perform fasciotomy is based on clinical findings and performed at a low level of suspicion. Biomarkers of muscle cell damage may help to identify and monitor patients at risk, similar to current routines for patients with acute myocardial infarction. This study will test the hypothesis that biomarkers of muscle cell damage can predict ACS in patients with tibial fractures.

Methods and analysis Patients aged 15–65 years who have suffered a tibial fracture will be included. Plasma (P)-myoglobin and P-creatine phosphokinase will be analysed at 6-hourly intervals after admission to the hospital (for 48 hours) and—if applicable—after surgical fixation or fasciotomy (for 24 hours). In addition, if ACS is suspected at any other point in time, blood samples will be collected at 6-hourly intervals. An independent expert panel will assess the study data and will classify those patients who had undergone fasciotomy into those with ACS and those without ACS. All primary comparisons will be performed between fracture patients with and without ACS. The area under the receiver operator characteristics curves will be used to identify the success of the biomarkers in discriminating between fracture patients who develop ACS and those who do not. Logistic regression analyses will be used to assess the discriminative abilities of the biomarkers to predict ACS corrected for prespecified covariates.

Ethics and dissemination The study has been approved by the Regional Ethical Review Boards in Linköping (2017/514-31) and Helsinki/Uusimaa (HUS/2500/2000). The BioFACTS study will be reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology recommendations.

Trial registration number NCT04674592.

Strengths and limitations of this study

- ► The first prospective study to investigate plasma levels of myoglobin and creatine phosphokinase in patients with tibial fractures with and without acute compartment syndrome (ACS).
- ► Multiple participating centres, including different hospital categories from two Nordic countries.
- ► Expert panel assessment of ACS.

INTRODUCTION

Acute compartment syndrome (ACS) is a serious complication in trauma. As the condition is difficult to diagnose and the consequences of a missed compartment syndrome are detrimental, decompressive fasciotomy is performed when there is a low level of suspicion, possibly often leading to unnecessary surgeries.[1]

ACS is caused by either a volume expansion of the muscles, for example, muscular swelling, or a decrease in the compartment space, for example, burn injuries, leading to increased intracompartmental pressure. The increased pressure, in turn, leads to decreased perfusion and, if left untreated, tissue necrosis.[2] ACS can emerge in a wide variety of locations, although most commonly it affects the lower leg due to its tight inelastic fasciae.[3] Tibial fracture is the most common injury associated with ACS, and ACS develops in 2%–8% of the cases.[2 4] The cardinal symptom of ACS is pain, which can be very difficult to differentiate from the pain caused by a fracture. The treatment for ACS is urgent surgical decompression of the affected muscle compartments through fasciotomy. However, fasciotomy involves a large incision of the skin and compromises the soft tissue envelope around the fractured bone. Therefore, fasciotomy has a profound negative impact on the possibilities for orthopaedic treatment of the fracture, increases the risk for complications,

prolongs hospital stays and drives up costs.[5–7] Therefore, correct and timely diagnosis is of the outmost importance for these patients.

Currently, ACS is diagnosed using a combination of physical findings and intra-compartmental pressure measurements. Each of these measures has inherent drawbacks in terms of making the correct diagnosis.[1 8 9] Specific pressure thresholds at which fasciotomy should be performed have been proposed.[9 10] However, studies have shown that up to 84% of patients with a tibial fracture exceed this pressure threshold without developing ACS.[11] A recent study has shown that perfusion pressure has low specificity,[12] and, furthermore, the pressure varies with distance to the fracture, making the interpretation even more difficult.[9] Inappropriate use of the method may, therefore, lead to unnecessary fasciotomies. Other promising diagnostic modalities include near-infrared spectroscopy (NIRS). Decreased tissue oxygenation levels correlate with increased intramuscular pressure.[13] NIRS can detect a sudden decrease in tissue oxygenation in patients with ACS,[14] although the reliability of NIRS in an injured leg remains uncertain and its role in the diagnosis of ACS has not been defined.[15] Biomarkers, including measurements of pH and intramuscular glucose might allow the identification of patients with impaired muscle metabolism due to ACS. Also, circulating microRNAs (miRNAs) might be a potential tool for the future.[16] However, none of these techniques is used in clinical routine today.

In the absence of good objective measures and a clear definition of when ACS is present, decision-making regarding fasciotomy relies on the judgement of the individual doctor, leading to significant variability (2%–24%) in the percentage of fasciotomies performed for ACS per surgeon in fracture patients.[17]

Similar to the diagnosis of acute myocardial infarction, whereby heart muscle-specific Troponin T is measured, markers of muscle cell damage (eg, P-myoglobin) may be used to diagnose objectively or to monitor ACS. The use of such markers has previously been deemed unfeasible on the basis that pathological levels of these markers could be attributed to sources other than the actual muscle compartment, for example, traumatic muscle damage and heart contusion.[18] Nonetheless, some studies have shown the potential of biomarkers to improve the diagnosis of ACS,[19 20] although never in the presence of a fracture.

We have recently shown that high intramuscular pressure coincides with high P-myoglobin levels and that myoglobin may be a relevant, yet unexplored diagnostic tool in ACS associated with trauma.[21]

Hypothesis

Plasma (P)-myoglobin and P-creatine phosphokinase (P-CK) can be used to predict ACS in patients with traumatic tibial fractures.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Traumatic tibial fracture* 15–65 years	Malignancy Acute myocardial infarction Kidney failure (GFR ≤35 mL/min) Muscle disease Paraplegia/tetraplegia

*Anylocation in the tibia, excluding solitary ankle fractures.
GFR, glomerular filtration rate.

Aims

Primary aim

To describe the diagnostic performances of P-myoglobin and P-CK to predict ACS in patients with traumatic tibial fractures.

Secondary aim

To compare the pathological changes in circulating miRNA and muscle biopsies with the levels of P-myoglobin and P-CK in fracture patients.

To compare changes in P-myoglobin and P-CK between fracture patients with ACS and non-fracture patients with ACS.

METHODS AND ANALYSIS

The study is a prospective, multinational, multicentre study. The study is currently running in Sweden at Linköping University Hospital, Vrinnevi Hospital in Norrköping, Höglandssjukhuset in Eksjö and Kalmar Hospital, as well as in Finland at Helsinki University Hospital. Additional hospitals may be included in the future.

Study population

Patients in the age range of 15–65 years who have suffered traumatic fractures of the tibia will be included. Exclusion criteria are listed in table 1.

Outcome measures

Primary

Myoglobin is an important myocyte-produced compound that is released into the bloodstream as the first enzyme to show increased levels following any type of muscle injury. Myoglobin becomes measurable when the protein binding capacity is exceeded after 1–3 hours. It peaks after 8–12 hours, and it is cleared from the plasma within 24 hours.[22]

The levels of CK in plasma increase within 12 hours of muscle injury, peak after 24–36 hours, and decrease at a rate of 30%–40% per day.[22] Both P-myoglobin and P-CK are routinely measured in the diagnosis and monitoring of rhabdomyolysis.[22] Therefore, facilities for the analysis of these enzymes are available in most clinical settings. The analyses are relatively cheap (roughly €30 per sample) and can be performed in less than 1 hour.

For this study, we chose a combination of these enzymes and a 6-hourly interval over a 24-hour or 48-hour period so as to be able to detect the postinjury peak of at least one of these enzymes (figure 1). Considering the urgency

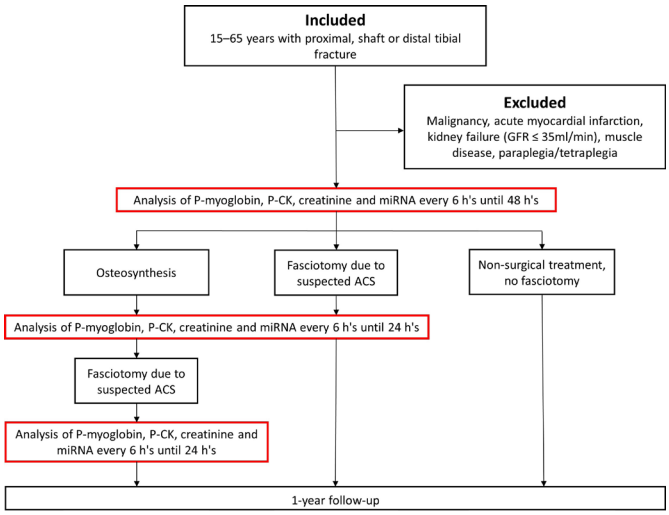

Figure 1 Flow chart of patient recruitment. ACS, acute compartment syndrome; GFR, glomerular filtration rate; P-CK, plasma-creatine phosphokinase.

of the diagnosis, we will primarily focus on an increase in the level of myoglobin as an early sign of muscle injury.

Secondary

We will collect blood samples for later analysis of muscle-specific miRNA at the same time intervals as for the primary outcome. Due to the rapidly evolving field of miRNA research, we abstain to prespecify specific miRNAs that will be used as objective measures of muscle damage.[23] At the time of surgery (internal fixation or fasciotomy), biopsies are taken at some centres for further histological analyses. Two biopsies are taken from the tibialis anterior muscle in the fractured leg, one close to the injury and one at a distance. One biopsy is taken from the same muscle in the uninjured leg (control). Biopsies are frozen within 30 min using liquid nitrogen-cooled isopentane.[24] For storage, the samples are kept at −80°C. Since P-myoglobin and P-CK can be affected by renal function,[25] we will analyse the level of serum creatine and the glomerular filtration rate (GFR). As sex, body weight and age can affect muscle volume, these parameters will also be collected. We will record the mechanism of injury (high or low energy), type of fracture (proximal, mid-shaft or distal and AO/OTA classification), trauma severity (solitary tibial fracture (with or without fibula fracture), tibial fracture with concomitant long bone fracture, tibial fracture in combination with multi-trauma), peri-operative findings of muscle viability (colour, consistency, contractility, capacity to bleed), and whether the muscle bulges at the point of incision. Stratified analyses for these subgroups will be performed if feasible.

Timing of blood samples

Plasma for assaying the levels of myoglobin and CK will be collected at those time-points at which the patient is at high risk to develop ACS (figure 1):

1. After the trauma, at admission to hospital: at 6-hourly intervals for a maximum of 48 hours or until definitive surgical fixation.
2. After definitive surgical fracture treatment: at 6-hourly intervals for 24 hours.
3. If there is suspicion of ACS at any other point in time, blood samples will be collected at 6-hourly intervals until fasciotomy is performed or the suspicion is dismissed, although no longer than 48 hours.
4. After fasciotomy, blood sampling will be continued at 6-hourly intervals for 24 hours.

Fasciotomy will be performed according to clinical routine praxis, as deemed feasible by the responsible surgeon.

Exploratory analyses

We recruit non-fracture patients with ACS of the lower leg to enable exploratory comparisons with fracture patients with ACS. Non-fracture patients will undergo the same sampling algorithm as fracture patients (figure 1). Patients with malignancy, acute myocardial infarction, kidney failure (GFR ≤35 mL/min), muscle disease, acute myocardial infarction, muscle disease, paraplegia/tetraplegia, any acute fracture or acute vascular events, will be excluded.

Blood sample analysis

The levels of P-myoglobin, P-CK and S-creatinine in patients at Linköping, Norrköping and Helsinki will be analysed at the respective hospital. Blood samples from Eksjö and Kalmar will be centrifuged, stored refrigerated and sent to Linköping for analysis. EDTA-tubes (for analysis of miRNA) will be centrifuged at 2500 rpm at room temperature for 10 min at each hospital. In the Swedish centres, the supernatant will be immediately and carefully removed, frozen in cryo tubes, and sent to and stored at −80°C until further processing. In Helsinki, the samples will be stored at the premises of the Helsinki Biobank prior to further analysis.

Expert panel assessment of ACS in patients with fasciotomy

Once collected, the data will be anonymised, uniformly compiled and reviewed by an independent expert panel of senior orthopaedic surgeons. The panel will retrospectively assess the clinical data (injury characteristics, radiographs, pain medication administered, details as to the surgical procedures). Thereafter, the panel will:

1. Specify whether or not the patient had an ACS.
2. Indicate the two most important factors contributing to that decision.
3. Determine if there are any missing data that might have influenced their decision.

The numbers of patients with ACS adjudged by the expert panel will be compared with the numbers of patients undergoing fasciotomy for ACS.

Follow-up

Patients will be followed clinically with individualised intervals according to routine care and at 1 year. The 1-year follow-up will include completion of the Lower Extremity Functional Score questionnaire and a clinical examination. The findings will be used for descriptive purposes, in

particular to detect patients who present with functional deficits that might be related to an undetected ACS. In all fasciotomised patients and those with suspected ACS-related functional impairment found during the clinical examination, we aim to perform bilateral MRI examinations of the lower leg to explore the possibility of MRI as an objective measure of ACS-induced tissue damage.

Sample size calculation and statistical analysis plan

We have performed two separate sample size calculations. The first calculation is based on pilot studies on patients with tibial fractures and patients with tibial fractures complicated by fasciotomy due to suspected ACS. The mean preoperative values for P-myoglobin were 289 and 1449 µg/L, respectively, with SD of 249 and 1044 µg/L, respectively. This corresponds to an effect size of 1.1 if we are conservative and use the largest SD of 1044 µg/L from both groups. Using this effect size of 1.1 with a two-sided test and alpha of 0.05, we need a sample size of 14 fracture patients undergoing fasciotomy due to suspected ACS to achieve 80% power. If we expect a fasciotomy prevalence of 5% of patients with tibial fractures, the expected number of non-fasciotomised patients is 266. In the second calculation, we assumed an improvement of the area under the curve (AUC) value from 0.5 (as good as chance) to 0.7 (acceptable diagnostic accuracy[26]), with an alpha of 0.05, a power of 80% and ACS prevalence of 5% in the study population. Under these assumptions, we require 16 fracture patients with fasciotomy due to suspected ACS and 311 non-fasciotomised patients. With 3–5 patients with fasciotomies due to suspected ACS presenting within the current study network every year, we estimate an inclusion period of 3 years. Inclusion will continue until 16 patients with tibial fractures and fasciotomies due to suspected ACS have been recruited, irrespective of the total number of recruited patients.

The difference in P-myoglobin levels between patients with fractures and suspected ACS, and non-fasciotomised fracture patients will be calculated with an independent samples Welch's t-test assuming different SD. The AUC will be used to identify the success of these biomarkers to discriminate fracture patients with ACS from those without.

Logistic regression analyses will be used to assess the discriminative ability of a combination of the two biomarkers to predict ACS, using correction for the following covariates: GFR; sex; body weight; age; trauma mechanism (high or low energy); fracture type (proximal, mid-shaft or distal and AO (Arbeitsgemeinschaft für Osteosynthesefragen)/OTA (Orthopaedic Trauma Association) classification); and trauma severity (solitary tibial fracture (with or without fibula fracture), tibial fracture with concomitant long bone fracture, tibial fracture in combination with multitrauma). Due to the limited sample size, we decide to use leave-one-out cross-validation for internal validation, which corresponds to analysis type 1b in the TRIPOD (Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) checklist.[27] A professional statistician (blinded to the clinical parameters) will perform the statistical analyses. All data will be anonymised and stored in secure servers within Region Östergötland, Sweden.

All primary comparisons will be performed between fracture patients with and without ACS.

Exploratory analysis will be performed between patients with suspected ACS, with or without a fracture. Separate statistical analyses will be performed for those patients who have undergone fasciotomies due to suspected ACS and those deemed as true ACS cases by the expert panel. When feasible, stratified subgroup analyses based on the above-mentioned covariates will be performed.

Trial status

Patient recruitment started at Linköping University Hospital on 1 April 2018. On 1 September 2019, a final study protocol was implemented at Linköping University Hospital and in subsequent months at Höglandssjukhuset district hospital Eksjö, Vrinnevi Hospital in Norrköping, and Kalmar Hospital. In January 2021, Helsinki University Hospital, Finland started to recruit patients. Currently, approximately 200 patients have been included.

Study time schedule

2021: Preliminary analysis of blood samples, muscle biopsies and miRNA to assess the quality levels of these samples.
2022: 300 patients included.
2023: Data analysis and manuscript writing.

Patient and public involvement

Neither patients nor members of the public are involved in the design, conduct, reporting, or dissemination plans of this study.

ETHICS AND DISSEMINATION

The study was approved by the Regional Ethical Review board in Linköping (Dnr. 2017/514-31) and the Ethical Review Board of the Hospital District of Helsinki and Uusimaa (HUS/2500/2000). Oral and written explanations will be provided to all eligible patients, and written consent will be obtained as soon as possible but no later than during clinical rounds the morning after enrolment. Patients might feel compelled to participate in the study as the treating surgeon usually is the same person that seeks the patient's consent. This is a problem that cannot be avoided in the context of recruitment performed in emergency situations.

As all the samples will be analysed in a blinded fashion, there is no risk that these values will disrupt the clinical decision-making process in the emergency situation. The risk for complications associated with study participation is low, and there is a potential diagnostic benefit. The study will increase the level of awareness and knowledge of medical staff. Therefore, regardless of the results, the implementation of the study will increase patient safety and, thereby, balance out any risks that study participation may entail.

If we will be able to define threshold values of P-myoglobin and P-CK for the detection of ACS with good diagnostic accuracy, these values could be implemented in clinical practice without delay. Specifically, these threshold values would allow the individual surgeon to decide to abstain from fasciotomy and instead observe the patient and follow the biomarker dynamics.

Author affiliations
[1]Department of Orthopaedics and Department of Biomedical and Clinical Sciences, Faculty of Health Science, Linköping University Hospital, Linkoping, Sweden
[2]Department of Orthopaedics and Traumatology, Helsinki University Hospital, and, University of Helsinki, Helsinki, Finland
[3]Department of Health Medicine and Caring Sciences, Linkoping University, Linkoping, Sweden
[4]Department of Orthopaedics, Eksjö, Region Jönköping County and Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden
[5]Division of Pediatric Neurology, Department of Women's and Children's health, Karolinska Institutet, Stockholm, Sweden
[6]Department of Orthopaedics, Norrköping, Östergötland County and Department of Biomedical and Clinical Sciences in Norrköping, Linköping University, Linköping, Sweden
[7]Department of Orthopaedics, Hennepin Healthcare, Minneapolis, Minnesota, USA

Twitter Ferdinand von Walden @ferdinandvw

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Contributors JS conceptualised the study idea. AN and JS planned and implemented the study at all the study sites. TI and LR planned and implemented the study at the Helsinki University Hospital. JL, AN and JS planned the statistical analysis. BA provided advice on biomarker handling and analysis and planned and implemented the study at Höglandssjukhuset Eksjö. FvW provided advice on biomarker handling and analysis. LF planned and implemented the study at Norrköping hospital. AS contributed to the overall design of the study. All the authors contributed to the design of the study and revised and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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ORCID iDs
Abraham Nilsson http://orcid.org/0000-0003-0256-008X
Thomas Ibounig http://orcid.org/0000-0001-9658-8571
Ferdinand von Walden http://orcid.org/0000-0003-1134-2252
Lasse Rämö http://orcid.org/0000-0003-4154-8462
Jörg Schilcher http://orcid.org/0000-0003-0677-9265

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