48 Metformin Rescues the Aging-induced Failure of Post-burn White Adipose Browning

Dalia Barayan, B.Sc., Carly M. Knuth, BSc, MSc, PhD (c), Marc G. Jeschke, MD PhD

University of Toronto, Toronto, Ontario; University of Toronto, Toronto, Ontario; U of T, Toronto, Ontario

Introduction: Severe burns are responsible for an estimated 300,000 deaths per year worldwide. While modern burn care has markedly improved survival for pediatric and adult patients, this is sadly not the case for one population: the elderly. Despite being the fastest-growing demographic in North America, burn patients over the age of 60 years have the highest mortality and morbidity rates. Recent evidence suggests that progressive aging induces several structural and functional alterations which impair the capacity of older trauma patients to adequately respond to stress. Indeed, it was discovered that reduced survival in elderly burn patients is associated with the failure to initiate the browning of white adipose tissue (WAT) —a hallmark of the systemic response to injury commonly observed in adults. Interestingly, the widely used hypoglycemic drug metformin has been found to protect against aging-induced metabolic decline in various pathological conditions. Thus, we investigated the anti-aging effects of metformin on the metabolic deterioration of post-burn WAT responses in elderly patients and mice after injury.
Methods: Human WAT was obtained from elderly patients admitted to our burn center. Elderly (75-week) mice received a full-thickness scald burn and/or daily intraperitoneal injections of metformin (100 mg/kg) for 7 days. The inguinal WAT was harvested for histological analyses. Mitochondrial respiration was measured via Seahorse XF96. Gene and protein expression was assessed via RT-PCR and western blot, respectively.
Results: Post-burn metformin treatment restores the thermogenic activation of WAT in elderly patients and mice, reflected by the increased expression of key browning markers, UCP-1 and PGC-1α ($p< 0.05$). This was accompanied by higher mitochondrial respiration, improved lipolysis ($p< 0.05$) and increased fat wasting ($p< 0.01$) relative to control counterparts. The anti-aging effects of metformin appeared to be mediated by AMPK, which consequently increased [NAD^+] ($p< 0.01$), thereby promoting activation of the longevity-specific enzyme Sirt-1 ($p< 0.05$).
Conclusions: Here, we show that post-burn metformin treatment effectively rejuvenates adaptive metabolic responses in elderly WAT by targeting key longevity pathways which rescue the age-dependent loss of being back to youthful levels. Our findings support the potential of anti-aging modalities to improve care and outcomes in elderly burned patients.

Correlative VII: Clinical Sciences: Wounds & Scars 1

C-251

49 Bromelain Based Enzymatic Debridement of Pediatric Deep Burns: Top Line Results of a Multicenter RCT

Yaron Shoham, MD, Ravi P. Narayan, Stan Monstrey, Henk Hoeksema, Giavonni M. Lewis, M.D. F.A.C.S., Manoj Kumar Jha, M.Ch. (Plastic Surgery), Shawn D. Larson, MD, FACS, Oleksii Kravtsov, Head of the department of burns, Elena M. HANGANU, Consultant in paediatric surgery, Horea G. Gozar, MD PhD Associate professor, Tam N. Pham, MD, FACS, Adam Singer, MD, Robert L. Sheridan, MD, FACS, FAAP, Paul M. Glat, MD, Frank Sander, Dhaval Bhavsar, MD, Lucy Wibbenmeyer, MD, FACS

Soroka University Medical Center, Beer Sheba, HaDarom; ESIC Medical College & Hospital, Faridabad, New Delhi, Delhi; Ghent University Hospital, GENT, Oost-Vlaanderen; University Hospital Ghent, Gent, Oost-Vlaanderen; University of Utah Burn Center, Salt Lake City, Utah; ABVIMS & Dr. RML Hospital, New Delhi, Delhi, Delhi; University of Florida College of Medicine, Gainesville, Florida; State Institution «Zaitsev VT Institute of General and Emergency Surgery of the National Academy of Medical Sciences of Ukraine», Kharkiv, Kharkivs'ka Oblast'; University of Medicine and Pharmacy, Faculty of Medical Bioengineering, Balneophysiotherapy and rehabilitation, Iași, Iasi; University of Medicine, Pharmacy, Science and Technology of Târgu Mureș, Targu Mures, Mures; University of Washington, Seattle, Washington; Stony Brook University Medical Center, Stony Brook, New York; Shriners Hospitals for Children Boston, Boston, Massachusetts; St Christopher's Hospital for Children, Bala Cynwyd, Pennsylvania; Center for Severe Burns with Plastic Surgery, Berlin, Berlin; University of Kansas Health System, Kansas City, Kansas; University of Iowa MD, FACS, Iowa City, Iowa

Introduction: Bromelain based debridement (BBD) of deep burns with a concentrate of proteolytic enzymes enriched in Bromelain is approved for use in adults in several regions worldwide. Children are a large part of the patient population in many burn centers around the world. Clinical trial experience and off label reports point to BBD safety and efficacy in children as well. The aim of this study was to further assess the safety and efficacy of BBD in children, in efforts to support regulatory approval for the use of BBD in children.
Methods: One hundred and forty five children aged 0-18 years old suffering from deep thermal burns between 1-30% TBSA were enrolled in a multicenter, multinational, open label, randomized, controlled phase III study. Seventy two children were randomized to eschar removal with BBD and 73 children to standard of care (SOC) surgical and/or non-surgical eschar removal methods, at the investigators' discretion. Patients who did not achieve complete eschar removal after BBD application were rescued with SOC eschar removal methods. Wound care after achieving complete

eschar removal was according to routine methods, at the investigators' discretion. Patients are currently in stages of long term follow-up, planned for a duration of >2 years. This abstract reports the top line results of the study including the first year of follow-up.

Results: Baseline characteristics were similar between the arms. The median age was 3.4 years in the BBD arm and 3.9 years in the SOC arm. The average burn area was 7.0±4.9 %TBSA in the BBD arm and 6.2±4.8 %TBSA in the SOC arm. The study met all 3 primary endpoints: Median time to complete eschar removal was 1 day for BBD and 6 days for SOC (p< 0.001), the percent wound area excised in order to complete eschar removal was 1.5% for BBD and 48% for SOC (p< 0.0001), and the MVSS scores at 12 months were 3.83 for BBD and 4.86 for SOC (non-inferiority endpoint). Secondary endpoints demonstrated 8.3% incidence of surgical excision to complete eschar removal for BBD and 64.4% for SOC (p< 0.0001), mean eschar removal associated blood loss of 32±284ml for BBD and 202±409 for SOC (NS), a 25.9% incidence of autografting in deep partial thickness wounds for BBD and 37.7% for SOC (p=0.054), and a mean percent area of deep partial thickness wound autografting of 15.9±38.6 for BBD and 22.8±43.7 for SOC (NS). Safety endpoints demonstrated a non-inferior time to complete wound closure (median 32 days for BBD, 34 days for SOC) and no significant safety issues were demonstrated during the study.

Conclusions: BBD was shown to be a safe and effective debridement agent in pediatric burns.

50 Rise of the (Learning) Machines: Artificial Intelligence for the Assessment of Adult Thermal Burns

Jeffrey E. Carter, MD, Herb A. Phelan, III, MD, MSCS, William L. Hickerson, MD, J. Michael DiMaio, MD, Jeffrey W. Shupp, MD, James H. Holmes, IV, MD, FACS

University Medical Center- New Orleans, New Orleans, Louisiana; LSUHSC-New Orleans Department of Surgery, New Orleans, Louisiana; Spectral MD, Avita Medical, AccessPro Med, Memphis, Tennessee; Baylor Scott and White, Dallas, Texas; MedStar Washington Hospital Center, Washington DC, District of Columbia; Atrium Health Wake Forest Baptist, Winston-Salem, North Carolina

Introduction: Burn depth assessment (BDA) is an essential component of the physical exam used in the treatment and triage of burn injured patients. And while many specialties incorporate labs and imaging to determine diagnoses, burn professionals must rely on a physical exam that is accurate in only 70-80% of cases. Our goal was to assess the accuracy of a new imaging technology called Multispectral imaging (MSI) combined with a machine learning algorithm to aid in rapid BDA. We present the results of the first multi-center study using this technology in adult burn injuries.

Methods: In a multi-center IRB-approved study, an MSI device was used to image subjects >18 years of age with thermal burn injuries. The imaging device captured a set of images measuring the reflectance of visible and near-IR light. Subjects were enrolled and imaged within 72 hours of injury with serial imaging as permitted. The images were used to develop a type of machine learning algorithm called a convolutional neural network (CNN) that could identify the regions of non-healing burn within an image. Non-healing burn areas were determined by a panel of three burn surgeons using two standards: a) images confirming 21-day spontaneous healing; or b) pathology reports detailing histologic changes from multiple punch biopsies taken prior to burn excision. From this data, an ensemble of eight separate CNN algorithms was used to automatically identify non-healing burn tissue. Training and test accuracies of the ensemble CNN were calculated using cross-validation at the level of the subject.

Results: One hundred (100) adults were enrolled and imaged. The population had a mean age 45.6 ± 16.7; mean TBSA 13.0 ± 9.3; and was 31% female. From these adults, 210 burn regions were serially imaged. The estimated performance result from the ensemble CNN for identification of non-healing burn regions was AUC of 0.96. Based on the ROC curve, an ideal threshold showed an accuracy of 92.0%, sensitivity 91.9%, and specificity 92.0%.

Conclusions: Our study demonstrates a non-invasive technology that rapidly determines an accurate DBA relative to traditional bedside exam. More accurate burn wound assessment could lead to avoiding unnecessary surgeries or delays in treatment and dramatic cost savings. Use of such a device in a disaster has additional value to better align a patient's burn care needs and available resources.