
FOOT AND ANKLE QUARTERLY

THE SEMINAR JOURNAL

Editor-in-Chief

Stephanie C. Wu, DPM, MSc

Editorial Advisors

George Andros, MD

David G. Armstrong, DPM, PhD

Christopher Bibbo, DPM, DO

John Buckholz, DPM

I. Kelman Cohen, MD, PhD

William J. Ennis, DO, MBA

Joshua Gerbert, DPM

Bruce L. Gewertz, MD

Lawrence J. Gottlieb, MD

Donald R. Green, DPM

Lawrence Harkless, DPM

Edwin J. Harris, DPM

Vincent J. Hetherington, DPM

Allen M. Jacobs, DPM

Warren S. Joseph, DPM

Keith B. Kashuk, DPM

Guido LaPorta, DPM

Lawrence Lavery, DPM, MPH

Gary M. Lepow, DPM

Benjamin A. Lipsky, MD, FACP,
FIDSA

E. Dalton McGlamry, DPM

John Stienstra, DPM

John Vanore, DPM

Lowell Scott Weil, DPM

Justin Wernick, DPM

Lawrence S. Zachary, MD

Expert Analysts

Marque A. Allen, DPM

Albert V. Armstrong, DPM

Richard Blake, DPM

Allan M. Boike, DPM

Richard T. Bouché, DPM

Albert E. Burns, DPM

Jonathan Contompasis, DPM

William H. Dabdoub, DPM

Howard J. Dananberg, DPM

J. Marshall Devall, DPM

Gary L. Dockery, DPM

Michael S. Downey, DPM

Ronald D. Edelman, DPM

John G. Fleischli, DPM

Josef J. Geldwert, DPM

Vincent Giacalone, DPM

Gary Gordon, DPM

George Gumann Jr., DPM

Kevin R. Higgins, DPM

Byron L. Hutchinson, DPM

A. Louis Jimenez, DPM

Bruce I. Kaczander, DPM

Steven R. Kravitz, DPM

Paul R. Langer, DPM

Sheldon I. Laps, DPM

Kieran T. Mahan, DPM

David E. Marcinko, DPM,
MBA, CFP

Bryan C. Markinson, DPM

David Mullens, DPM

Steven T. Palladino, DPM

Martin M. Pressman, DPM

Douglas H. Richie Jr., DPM

Barry I. Rosenblum, DPM

Jeffrey Ross, DPM, MD

Thomas S. Roukis, DPM, PhD

John Ruch, DPM

Amol Saxena, DPM

Harold D. Schoenhaus, DPM

John M. Schuberth, DPM

Nathan H. Schwartz, DPM

Barry Scurren, DPM

Steven Smith, DPM

Steven M. Spinner, DPM

John S. Steinberg, DPM

Mark A. Tozzi, DPM

Ronald L. Valmassy, DPM

H. John Visser, DPM

Harold W. Vogler, DPM

George F. Wallace, DPM

John H. Walter Jr., DPM

Joseph S. Werner, DPM

James S. Wrobel, DPM

Kerry Zang, DPM

FOOT AND ANKLE QUARTERLY: The Seminar Journal

NOTE TO SUBSCRIBERS

FOOT AND ANKLE QUARTERLY is a quarterly multimedia program designed to deliver all of the latest developments on the foot and ankle in a readily-accessible form.

FOOT AND ANKLE QUARTERLY consists of:

- Lectures and case studies in CD format
- A journal containing original articles and condensations with expert commentary as well as supporting visual material for the audio lectures and case studies
- A printed self-test questionnaire
- A **FOOT AND ANKLE QUARTERLY** binder to store the CDs and journals each year

CPME APPROVAL

Data Trace Publishing Company is approved by the Council on Podiatric Medical Education (CPME) as a sponsor of continuing education in podiatric medicine. **Foot and Ankle Quarterly** is a 24-credit-per-year program. Credits will be evenly distributed across issues 1, 2 and 3 (8 credits per issue).

LETTERS TO THE EDITOR

We welcome your comments, criticisms, or suggestions. Please address letters to:

Managing Editor
FOOT AND ANKLE QUARTERLY
P.O. Box 1239
Brooklandville, MD 21022-1239

FOOT AND ANKLE QUARTERLY subscription rates for 2019 are:

- Personal subscription \$219/year (add \$29 shipping for US; add \$34 shipping for Canada; add \$80 for foreign shipping)
- Resident subscription \$95/year (add \$29 shipping for US; add \$34 shipping for Canada; add \$80 for foreign shipping)
- Libraries and institutions \$298/year (add \$29 shipping for US; add \$34 shipping for Canada; add \$80 for foreign shipping)
- Multi-users \$192 per additional credit applicant per year; \$48 per/6-credit issue; \$64 per/8-credit issue
- Single issues are available for \$69 plus shipping for 6-credit issues; \$88 plus shipping for 8-credit issues (rates subject to change without notice).

TO ORDER FOOT AND ANKLE QUARTERLY:

Call toll-free 1-800-342-0454 or write to:

Data Trace Publishing Company
P.O. Box 1239
Brooklandville, MD 21022-1239
www.datatrace.com

FOOT AND ANKLE QUARTERLY: The Seminar Journal (ISSN 1068-3100) is published quarterly; one volume per year beginning with the Spring (Number 1) issue by Data Trace Publishing Company, P.O. Box 1239, Brooklandville, MD 21022-1239. (Formerly *PODIATRY TRACTS*, ISSN 0894-6116).

Foot and Ankle Quarterly is indexed in the *Cumulative Index to Nursing and Allied Health Literature*.

Frequency: Quarterly, one volume per year. Printed on acid-free paper in the USA.

Change of Address: Publisher must be notified 60 days in advance of address change. Send change of address to the above address. Include old mailing label, if possible, and allow at least four weeks for the change to take effect.

Postmaster: Send address changes to **Foot and Ankle Quarterly**, P.O. Box 1239, Brooklandville, MD 21022-1239.

Claims for Missing Issues: Claims for missing or damaged issues must be made within 60 days of publication date of each issue in the US and 90 days outside the US. Please write to address above.

To Order: New subscriptions are entered to begin with the Spring (#1) issue. Orders should be mailed to: Data Trace Publishing Company, P.O. Box 1239, Brooklandville, MD 21022-1239. Please indicate personal or institutional status. Visit Data Trace online at www.datatrace.com or call toll free **800-342-0454** or **410-494-4994** outside the US to place an order. Checks should be made payable to Data Trace Publishing Company. We accept Visa, Mastercard and American Express.

Copyright © 2019 by Data Trace Publishing Company. All rights reserved. Reproduction or translation of any part of this work beyond that permitted by Section 107 or 108 of the United States Copyright Law without the permission of the copyright owner is unlawful. No portion(s) of the work(s) may be reproduced without written consent from Data Trace Publishing Company. Permission to reproduce copies of articles for non-commercial use may be obtained for a fee of \$22 per copy from the Copyright Clearance Center, 222 Rosewood Drive, Danvers, MA 01923, 978-750-8400, www.copyright.com.

The ideas and opinions expressed in *Foot and Ankle Quarterly* are those of the authors and do not necessarily reflect those of the Editor or the Publisher. Publication of an advertisement or other product mentioned in *Foot and Ankle Quarterly* should not be construed as an endorsement of the product of the manufacturer's claims. Readers are encouraged to contact the manufacturer with any questions about the features or limitations of the products mentioned. The Publisher does not assume any responsibility for any injury and/or damage to any persons or property arising out of or related to any use of the material contained in this periodical. The reader is advised to check the appropriate medical literature and the product information currently provided by the manufacturer of each device or of each drug to be administered to verify the dosage, the method and duration of administration, or contraindications. It is the responsibility of the treating physician or other healthcare professionals, relying on independent experience and knowledge of the patient, to determine drug dosages and the best treatment for the patient.

FOOT AND ANKLE QUARTERLY

Volume 30

Regenerative Medicine

Summer 2019

Number 2

Guest Editor: Marlene Reid, DPM

ISSN # 1068-3100

Editorial

Marlene Reid, DPM

vii

FEATURE ARTICLE

Podiatric Applications of Regenerative Medicine: Where we Came From,
Where we Are and Where we Are Going

Marlene Reid, DPM

73

CONDENSATIONS/COMMENTARIES

Direct Radiofrequency Application Improves Pain and Gait in
Collagenase-Induced Acute Achilles Tendon Injury

Commentary by *Alex Kor, DPM, MS*

82

A Biomechanical Assessment of Tendon Repair after Radiofrequency Treatment

Commentary by *James Ratcliff, DPM*

86

The Effects of Irreversible Electroporation on the Achilles Tendon: An
Experimental Study in a Rabbit Model

Commentary by *Britton S. Plemmons, DPM*

90

The Placenta: Applications in Orthopaedic Sports Medicine

Commentary by *Howard G. Osterman, DPM*

93

The Use of Decellularized Human Placenta in Full-Thickness Wound Repair and
Periarticular Soft Tissue Reconstruction: An Update on Regenerative Healing

Commentary by *James M. Cottom, DPM and Colin T. Graney, DPM*

98

The Bio in the Ink: Cartilage Regeneration with Bioprintable Hydrogels and
Articular Cartilage-Derived Progenitor Cells

Commentary by *Stephen Brigido, DPM*

101

Topical Review: MACI as an Emerging Technology for the
Treatment of Talar Osteochondral Lesions

Commentary by *Lawrence A. DiDomenico, DPM and Mohammed K. Hassan, DPM*

105

Matrix-Associated Stem Cell Transplantation (MAST) in Chondral Defects of the First
Metatarsophalangeal Joint is Safe and Effective: Two-Year Follow-Up in 20 Patients

Commentary by *Britton S. Plemmons, DPM*

109

Sports Medicine and Platelet-Rich Plasma Nonsurgical Therapy

Commentary by *Patrick A. McEneaney, DPM*

112

Synthesis, Development, Characterization and Effectiveness of Bovine Pure Platelet Gel-Collagen-Polydioxanone Bioactive Graft on Tendon Healing Commentary by <i>Lawrence A. DiDomenico, DPM and Emlyn K. Forsung, DPM</i>	116
Regenerative Rehabilitation: Applied Biophysics Meets Stem Cell Therapeutics Commentary by <i>Lawrence M. Kosova, DPM</i>	121
Adipose-Derived Stem Cells in Orthopaedic Pathologies Commentary by <i>Stephen Brigido, DPM</i>	125
Lipofilling for Functional Reconstruction of the Sole of the Foot Commentary by <i>David G. Armstrong, DPM and Laura Shin, DPM, PhD</i>	130
AUDIO LECTURE I	
Plantar Fascia Treatment Options in the 21 st Century <i>Marlene Reid, DPM</i>	134
AUDIO LECTURE II	
Regeneration vs. Repair: What's the Difference? <i>Stephen A. Brigido, DPM</i>	136
CME QUESTIONNAIRE	138

Synthesis, Development, Characterization and Effectiveness of Bovine Pure Platelet Gel-Collagen-Polydioxanone Bioactive Graft on Tendon Healing

Article by Moshiri A, Oryan A and Meimandi-Parizi A. J Cell Mol Med. 2015 Jun; 19(6): 1308-1332.

Commentary by **Lawrence A. DiDomenico, DPM and Emlyn K. Forsung, DPM**

The authors certify that they have no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

CONDENSATION

Purpose of Study

To investigate whether bovine platelet gel (BPG) can accelerate tendon repair

Approach

Extraction of the collagen type I from bovine tendon and its purity was confirmed by SDS-PAGE, followed by electrospinning. The electrospun collagen fibers were obtained by electrospinning the collagen molecules onto a dual-plate device. In order to produce the tridimensional collagen gel, the electrospun bovine tendon type I collagen molecules were mixed with electrospun collagen fibers and polymerized in an incubator at 4 degrees Celsius. During the polymerization, the collagens were then aligned under 12 Tesla magnetic fields. The composite materials were cut into several pieces according to the size and shape of the rabbit's Achilles apparatus followed by crosslinking using irradiation to increase the mechanical properties of the scaffold, so that it could hold the surface tensions.

The bioimplant (CI-PDS) was prepared by wrapping a polydioxanone sheet around each collagen piece. It was left for drying at room temperature to avoid any in vivo tissue reaction with the chemical solvents. The final product was repeatedly washed to maintain its sterility until surgery. The peripheral blood samples were collected from healthy bovines which were free of any

infective diseases, and centrifuged which resulted in the formation of three layers: the red blood cells, white blood cells or platelets and plasma. The plasma and the buffy coat layers were centrifuged again, which also resulted in the production of three layers: white blood cells at the bottom, platelet-rich plasma (PRP) at the middle and platelet-poor plasma (PPP) at the top. The PRP and PPP were studied under stereomicroscope to confirm that the samples were free from bovine WBCs and RBCs.

Finally, the PRP and PPP preparations were lyophilized and pulverised into a sterile powder. The powder was added to 0.9% NaCl to achieve a concentration of 2,000,000 per each μl . The fully-dehydrated CI-PDS were placed in a plate containing a solution of protein rich platelets which led to the absorption of the solution to the scaffold. The attachment of the platelets to the collagen fibers was confirmed by SEM, TEM and light microscopy. Based on the morphology of the scaffolds, three groups were observed: CI, CI-PDS and CI-PDS-BPG. The coagulation profiles, activated partial thromboplastin time, prothrombin time, degradation rate and levels of platelet growth factor were determined. The functional activity of the platelets was determined by platelet aggregation testing, live and dead cell assay and immunofluorescence microscopy.

The in vivo study was conducted on 160 male New Zealand rabbits which were randomly assigned to experimental and control groups (CI, CI-PDS and CI-PDS-BPG). Tendon injury was inflicted by making a 2-cm excision of the Achilles and the paratenon. Surgical reconstruction involved producing a 2-cm gap between tendons and insertion of implants into the gaps. The animals in each group were evaluated at 60 and 120 days after tendon injury and surgical reconstruction. There were a pilot group which consisted of 40 rabbits, they were also randomly assigned to four groups and were evaluated at 20 and 40 days after injury to study the host-implant interactions. The pre-euthanasia assessments were conducted on animals before anaesthetizing and finally euthanizing them by using intra-cardiac injection of 1 mg/kg gallamine triethiodide. The features of the healing tendons of the animals after euthanasia were assessed for the following characteristics: dry matter content, water uptake and delivery characteristics, gross morphological, histopathological and scanning electron microscopic features.

What Investigators Accomplished

- The biconvex discoid shape of the non-activated platelets produced after first step centrifugation (PFSC), platelets produced after second step centrifugation (PSSC) and platelets produced after lyophilisation and saline solving procedure (PLSSP) were observed having 2-3 μm diameter. The activated platelets in the platelet gel had pseudopodia emission which was confirmed by TEM and SEM. The number of platelets observed in the CI-PDS-BPG was 2×10^6 . The implant was made to absorb the platelets and the structure of the platelets which was confirmed by SEM, TEM and light microscopy. The amount of activated platelets to total platelets was $89.61 \pm 6.54\%$ which indicated that the activation method

was effective. No significant difference concerning partial thromboplastin time was observed between NBC and PFSCs and also between PFSC and PSSCs, whereas the prothrombin and clotting time increased significantly when compared to controls. The degradation rate of the PRP significantly decreased after the centrifugation when compared with controls. Similarly, the degradation rate of BPG decreased because of LSSP on comparing with controls.

- There was no significant difference between the LTA of PFSCs and PSSCs and between the LTA of the PSSCs and those of PLSSPs in light transmission aggregometry. The growth factors platelet-derived growth factor (PDGF)-AA, -AB, -BB and insulin-like growth factor 1 (IGF-1) were higher than that of PFSCs. The levels of growth factors of the PLSSPs were reduced when compared to PSSCs, the activation of the PLSSPs to the platelet gel increased the levels of growth factors when compared to the controls. The BPG increased the number of viable cells in the CI-PDS-BPG compared to the CI and CI-PDS, improved the cellular proliferation, cell maturation and matrix production.
- The BPG lead to a superior distribution of the cultured fibroblasts inside the scaffold and the cells. The immunofluorescence microscopy, SEM and light microscopy confirmed there were no significant differences observed between numbers of the cultured fibroblasts in different parts of the CL-PDS-BPG scaffolds. The clinical examination revealed that the treatment with BPG improved the tarsal flexion degree, weight distribution, heel and toe position, pain on palpation and swelling of the injured area compared with the animals which were untreated or treated with CI or CI-PDS. No significant differences were observed between the transverse diameter of the injured and contralateral tendons after the operation. Although after the implantation of the prosthetic implant, the transverse diameter of the injured tendons increased on days seven and 14, however it gradually decreased until day 120 after injury. Even positive results were observed in regards of surface temperature in the animals after the implantation when compared to control.
- The treatment with BPG improved the echogenicity, homogeneity, peritendinous adhesion, regeneration volume, intensity of the peritendinous adhesion and regenerative proportion compared to the control, collagen and collagen-PDS treated groups. There were no significant changes observed in the number of RBCs between multiple groups but after the implantation of prosthetic implants in tendon defects the number of leucocytes decreased in all treated groups compared to the control group.
- The treatment with BPG increased the scoring values for the development of peritendinous adhesion, hyperaemia, general appearance of the neotendon, muscle atrophy and muscle fibrosis compared to the control, CI and CI-PDS treated groups. The treatment with BPG significantly decreased total cellularity, total fibroblast, immature fibroblast and lymphocyte and even increased number of mature fibroblast and fibrocyte, macrophages, blood vessels and collagen density compared to control tendons, CI

tendons and CI-PDS observed at 60 days after injury. The cellularity, total fibroblasts, number of immature fibroblast, inflammatory cells, blood vessels and cell density decreased in all the groups when compared to 60-day levels after injury. At 60 and 120 days after injury, the treatment with BPG significantly increased transverse diameter density of the collagen fibrils, fibers and fiber bundles compared to controls, and it improved the scored values of the tissue alignment, maturity of the collagen fibrils and crimp pattern compared to the control, CI and CI-PDS treated groups. It was also observed that after the implantation, the inflammation and the transverse diameter of the injured area increased which accelerated fibroplastic response. The treatment with BPG significantly increased the dry matter and hydroxyproline contents of the injured area compared the other groups. The animals which were treated with BPG had a close behaviour of water uptake and water delivery to normal tendons, CI and CI-PDS treated tendons score.

Investigators' Observations

This study suggests that BPG is an “accessible, reliable, cost-effective and powerful healing promotive source of the platelets and growth factors” and can be used as an alternative option to autogenous and allogeneous forms of platelets, and that CI-PDS-BPG is a valuable graft option over classic grafts for managing tendon injuries.

REFERENCES

- Beals TC, Severson EP, Kinikini D, Aoki S. Complex Achilles reconstruction for massive soft tissue loss: allograft, autograft, and use of a temporary cement spacer. *J Orthop Trauma*. 2010 Aug;24(8):e78-80.
- Bosch G, Moleman M, Barneveld A, et al. The effect of platelet-rich plasma on the neovascularization of surgically created equine superficial digital flexor tendon lesions. *Scand J Med Sci Sports*. 2011 Aug;21(4):554-561.
- Bullocks JM, Hickey RM, Basu CB, et al. Single-stage reconstruction of Achilles tendon injuries and distal lower extremity soft tissue defects with the reverse sural fasciocutaneous flap. *J Plast Reconstr Aesthet Surg*. 2008;61(5):566-572.

COMMENTARY

This article can have a big influence on the future of acute tendon repair. The idea of having the availability of a scaffold for repair of the Achilles tendon is needed in particular cases with great ruptures/tears and significant tissue loss. This study showed the effectiveness of bovine pure platelet gel-collagen-polydioxone bioactive graft in acute tendon injury in animal studies.

Treatment with BPG significantly enhanced the scoring values for the development of peri-tendinous adhesions. It also significantly increased the transverse diameter and density of the collagen fibrils, fibers and fiber bundles, and sooner differentiated the collagen fibrils to fibers and fibers to fiber bundles compared to the controls. The results of the study showed that the

BPGs, when embedded within collagen implant with polydioxanone (artificial tendon), significantly enhances cytocompatibility of the implant at in vitro level but also improves scaffold biocompatibility and biodegradability in vivo. BPG was proven to be successful.

The reluctance in using an off-the-shelf product in acute tendon injury will be due to the availability of PRP from the patient, the reaction that it may cause and the expense. Compared to off-the-shelf BPG, PRP is readily available and is free. PRP has also been proven to be effective in facilitating tendon healing. As it comes from the patient, PRP has no chance of host reaction. Even though this study shows that BPG has a great potential, it will need to be tested in humans in a clinical trial setting (most foot and ankle surgeons will be reluctant to try a product which has not been tested and approved by the FDA).

The results of this study may have an impact in the in the treatment of acute tendon injuries in the future. As of now, the readily available PRP from patients will remain the standard, compared to an off-the-shelf product such as BPG.