International Institute for Race Medicine

ENDURANCE AND SPORTS MEDICINE

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In this Issue:

Endurance and Sports Medicine

FOUNDER William O. Roberts, MD

The mission of the International Institute for Race Medicine (IIRM) is to promote the health and safety of athletes participating in endurance events through education, research, and the development of medical best practices.

Opinions expressed in *Endurance and Sports Medicine* are not necessarily endorsed by the IIRM.

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IIRM NEWS

Exciting things are happening at the International Institute for Race Medicine (IIRM) with continuing education activities and upcoming partnerships.

IIRM in DC and Boston

We just wrapped up our 2018 Sports Medicine Conference Series in Washington, DC, with close to 150 individuals in attendance. The participants attended the two-day program filled with lectures and workshops and then had the opportunity to volunteer in the medical tents at the Marine Corps Marathon. Among the lecture topics were gait retraining for running injuries, exertional hyponatremia, cardiovascular considerations for runners, and advanced therapies for injury. We also had multiple workshops including how to manage conditions such as exercise-associated collapse, cardiovascular arrest, and exertional heat stroke; ultrasound for the runner; and VO2 max testing and zone training implementation. We hope you will join us in DC next year!

We are returning to Boston in April with a one-day sports medicine conference being held at the Northeastern University Bouvé College of Health Sciences on April 13, from 8:00 am to 5:00 pm. See the back page of this journal for more details.

(continued on page 21)

CONTENTS

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LETTER FROM LEADERSHIP

The IIRM and Matthew Good Foundation

My brother Matt and I were strong runners in school. We both won our respective years at cross country and did well in longer distance athletics, as well. Through our 20s, however, we didn't really run competitively. By age 32 Matt had worked his way up in the family shipping business, which has been in our family since 1833. He was the joint managing director and there is no doubt in my mind that he would have been named chairman by now.

In late 2010 Matt and I were planning to launch a foundation funded by our family business. I would be the chairman of this foundation and he would continue to run the family business; we would work side-by-side. Around that time Matt was asked to run the Humber Half Marathon to help raise money for a school in Uganda. He took up the challenge and began to train. Although he hadn't run in many years, Matt liked a challenge and it was quickly apparent he would be able to complete the race in around 1:30.

Matt (left) and Tim on a climbing trip in Spain in 2010.

The race was scheduled for June 26, 2011, and his training went well in the cool climates of British spring time. However, a few days before the event, forecasts were showing a freak heatwave. On the day of the race, it started off a little cloudy but soon cleared with the wind dropping to nothing. I do not know what the WBGT was but the temperature was 82 degrees Fahrenheit (28 degrees Celsius) in the shade.

The Humber Half is renowned as a difficult course as it crosses the one-mile long Humber Suspension Bridge twice and has many long hills with false horizons. Unfortunately, the medical care on race day was not up to par. It was provided by St John Ambulance, an organization with first aid training but little knowledge of race medicine. Additionally, the medical provision on the suspension bridge was poorly planned.

Matt collapsed in the center of the bridge at mile 12. He went into cardiac arrest and had likely passed before he was evacuated to the hospital. Initially the hospital recorded his passing as being due to a cardiac abnormality; however, once I began posting on forums to search for runners on the scene, I discovered some facts that made me question the death record. Matt was staggering and appeared to have an altered state of consciousness prior to his collapse. He was offered water but refused

and told them to pour it over his head, instead. (I wonder, was that because he feeling a severe headache?) He then passed out and a doctor running the race began CPR. It took approximately 5 to 10 minutes for the defibrillator to reach the scene since a motorcycle first aider had to ride one mile up the bridge and then do a U-turn to reach the other side.

During first aid attempts a drip was applied and a witness heard the medics say something like "Get some water in him." The medic administering the IV replied, "He's already full of water." I'm not a medical professional and I cannot say if it is possible to determine the hydration status of a patient whilst administrating fluid via IV; however, these witness accounts prompted me to share these findings with the coroner's office. They then decided that a post-mortem would be wise. Following an examination, it was concluded his heart was healthy and he passed from brain stem compression as a result of cerebral oedema.

> Comments from the coroner: *The findings in the brain are those of diffuse cerebral oedema with a central pressure cone and evidence of transtentorial herniation. The brain stem is oedematous and there is evidence of tonsillar descent into foramen magnum. This tonsillar descent, however, has not been of sufficient duration to produce tonsillar necrosis or Duret haemorrhages. The cause of the cerebral oedema is uncertain.*

I am happy to share the full post mortem results to any IIRM member who feels it will help their understanding of race medicine and/or hyponatremia. Some may suggest the likelihood of becoming hyponatremic in only an hour and 30 minutes is low but I have a hard time imagining what else could have caused cerebral oedema.

Here are some additional thoughts I have regarding Matt's collapse:

- He was a salty sweater and perspired more than myself whilst running.
- He was undoubtedly pushing himself in that last mile or two.
- He had always liked to hydrate even out-of-sport and would always have a pint of water by his bed. Could he have, perhaps, over-hydrated in preparation for the race?

We had already set into motion the development of a foundation to be launched in September 2011 and following Matt's passing, I took the decision to name the foundation after him. The Matthew Good Foundation's involvement with the IIRM started when I contacted KSI Executive Director and IIRM Advisory Board Member Douglas Casa, PhD, ATC, about what happened. Doug highlighted that immediate cardiac arrest is very uncommon for heat stroke and this led me to further lines of inquiry and eventual discussions with IIRM Executive Director Chris Troyanos, ATC. During these discussions, I began to feel it was important to support a non-profit organization whose goals were to improve medical care provided at endurance events; I chose the IIRM as the foundation's first project (the Matthew Good Foundation now supports many causes and charities as part of our mission).

We had already set into motion the development of a foundation to be launched in September 2011 and following Matt's passing, I took the decision to name the foundation after him.

The foundation initially helped with funding to develop the IIRM brand and its website design. It later provided funding to research and collate the IIRM's 92-page medical care manual with Stephen Mears, PhD, at Loughborough University. In addition, Chicago Marathon Medical Director and IIRM Executive Board Member George Chiampas, DO, allowed us to film and produce educational videos at the Chicago Marathon. Dr. Chiampas and his medical team were exceptionally accommodating and knowledgeable. Most recently, we provided funding to help support the excellent work Barbara Baldwin, MPH, is doing to keep our initiatives moving forward.

The Matthew Good Foundation would be very happy to see the IIRM progress in helping races in the UK, with the possibility of allowing smaller races to have access to the manual and educational video free of charge. We would also like to see the IIRM continue to engage in its own research and development of best practice whilst being the "go to" place for race medical directors, runners, the press, and commercial entities with regard to safety in endurance sports.

The future of the IIRM and what it can accomplish is dependent upon the support of its leadership and members.

The future of the IIRM and what it can accomplish is dependent upon the support of its leadership and members. There is still much work we need to do but there is good news—we are gaining momentum and starting to get the attention of key target audiences. This, in turn, is helping us address our mission to promote the health and safety of athletes participating in endurance events worldwide. It is my hope that this will help us save lives.

My special thanks go to Chris Troyanos, Dr. Doug Casa, Dr. George Chiampas, and Dr. Pierre d'Hemecourt for their assistance, enthusiasm, and continued support as we work together to make a difference in the racing world.

Best regards,

Tim Good
Chairman, Matthew Good Foundation
Advisory Board Member, IIRM

Regenerative Medicine Options for Chronic Musculoskeletal Conditions: A Review of the Literature

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Abstract

Regenerative medicine as applied to musculoskeletal injuries is a term used to describe a growing field of musculoskeletal medicine that concentrates on evidence-based treatments that focus on and augment the body's endogenous repair capabilities. These treatments are targeted at the specific injury site or region of injury by the precise application of autologous, allogeneic or proliferative agents. Focusing on the repair of chronic musculoskeletal injuries, this paper will discuss both background and emerging theories in regenerative medicine, as well as specifically address developments in the clinically-relevant literature on specific treatments including: prolotherapy, platelet-rich plasma, autologous mesenchymal stems cells, alpha 2 macroglobin, and human tissue-derived allograft products.

Keywords: Regenerative medicine, platelet-rich plasma, mesenchymal stem cells, prolotherapy, micro-fragmented adipose, bone marrow concentrate, alpha 2 macroglobin

Introduction

The term "regenerative medicine," as applied to musculoskeletal injuries, describes a rapidly growing field of musculoskeletal medicine that employs evidence-based treatments that focus on augmenting the body's endogenous repair capabilities both at the specific injury site and at the region of injury by the precise application of autologous, allogeneic or proliferative agents. World-wide, the market for regenerative medicine is expected to be over 67 billion dollars in spending on biologics and cell therapies by 2020 (1).

Specifically, regenerative medicine also stands in contrast to treatment modalities that impair the body's ability to facilitate endogenous repair mechanisms such as anti-inflammatory drugs (2,3); destructive modalities (e.g., radio frequency ablation of nerves, botulinum toxin injections) (4); and surgical methods that permanently alter the functioning of a joint, including joint fusion, spine fixation, and partial or total arthroplasty. When compared to other allopathic options (including knee and hip arthroplasty with a 90-day mortality rate of 0.7% in the Western hemisphere) (5), regenerative medicine treatment modalities have a lower incidence of adverse events with a growing body of statistically significant medical literature illustrating both their safety and efficacy (6).

When evaluating regenerative treatment options, it is reasonable to start by evaluating the medical evidence for currently accepted medical options for subacute and chronic musculoskeletal injuries.

Non-steroidal anti-inflammatory drugs (NSAIDs), as well as corticosteroid preparations, are widely prescribed for acute and chronic pain conditions. However, according to the Cochrane Database Systemic Reviews, there is poor justification in the medical literature to indicate they promote improved long-term tissue healing (7,8). NSAIDs may interfere with tissue healing (9,10). In 2017, a well-executed randomized controlled trial (RCT) with two-year follow-up comparing intra-articular injection of corticosteroids to normal saline injections for the treatment of knee osteoarthritis showed no association with improvement in pain. In addition, the steroid treated knees showed MRI evidence of accelerated osteoarthritis (11). The combination of local anesthetic and corticosteroid has substantial evidence showing that corticosteroids are toxic to chondrocytes both in vivo and in vitro (12,13). Regarding the use of corticosteroids in treating tendinopathy, in 2010 Coombes and colleagues published a meta-analysis of 41 RCTs that concluded that "at four weeks post-injection, the non-injection groups had better pain and function" (14). In addition, a randomized controlled trial

comparing corticosteroid to placebo (saline) injections demonstrated worse outcomes in the corticosteroid injection group after one year (15).

The physiologic argument for using anti-inflammatory medications for the treatment of tendinopathies was called into question, if not refuted, in a landmark publication by Kraushaar and Nirschl in 1999. Using electron microscopy sections of human lateral epicondyle tendons clinically identified as tendinitis, they demonstrated that there was a conspicuous absence of cells associated with inflammation present in what previously, and inaccurately, had been called "tendinitis" (a term implying inflammation). They successfully demonstrated that the underlying pathology, instead, represented a chronic degenerative condition referred to as "tendinosis" (16).

In the case of spine injections, including epidural steroid injections in the setting of subacute and chronic lumbar pain, an updated 2009 Cochrane review of 18 RCTs concluded "there is currently insufficient evidence to support the use of [corticosteroid] injection therapy in subacute and chronic low-back pain" (17).

Many standard orthopedic surgeries, including arthroscopic surgery for the repair of knee meniscal tears in patients over the age of 40, have been shown in a recent meta-analysis of nine RCTs to be no better than sham surgery or conservative treatment (18,19).

Opioid therapy has also long been a mainstay of treatment for chronic non-neoplastic musculoskeletal pain. However, chronic narcotic therapy has inadvertently contributed to a national epidemic of opioid-related deaths (20) in addition to the known adverse effects of opioid-induced hyperalgesia, constipation, and lack of long-term efficacy or improved quality of life (21).

These publications in high-impact peer reviewed medical journals may cause physicians treating musculoskeletal disorders to consider potential alternative treatments, including safe, physiologically sound treatment options that are supported by reasonable medical evidence.

The regenerative medicine treatment model focuses on shifting the balance from catabolism and tissue degeneration towards anabolism and tissue repair on a local and regional level. The body is capable of self-repair. In the setting of chronic injury there are several reasons for inadequate or failed self-repair:

1) The body fails to recognize an injury and mounts an effective healing response.

2) The repair mechanism is overwhelmed by ongoing tissue insults such as chronic repetitive movements without adequate recovery, ligamentous laxity resulting in pathologic joint movement, and functional movement disorders resulting in pathologic movement.

3) The repair mechanisms are inhibited by a sub-optimal healing milieu. Factors contributing to a catabolic, sub-optimal healing milieu include, but are not limited to: exposure to toxins (including many pharmaceuticals), poor diet, obesity, lack of regular exercise, chronic systemic inflammation, chronic infection, poor sleep, hormonal deficiencies, and chronic stress (22,23).

Each of these reasons for failure to self-repair is a potential target for regenerative medicine and counseling.

In addition, as we age, the body moves towards senescence with a slow shift from a balanced catabolic/anabolic environment to one that slightly favors catabolism, thus resulting in gradual tissue degeneration. At some point, this slow senescence becomes clinically manifested in the form of chronic injuries. One goal of regenerative medicine treatment is to augment the anabolic environment through the stimulation of native and natural processes.

Dr. Sean Mulvaney performing an ultrasound-guided bone marrow aspirate concentrate injection.

Many regenerative medicine techniques rely on precise injections of autologous, allogeneic or proliferative agents that initiate (or re-initiate) a productive healing cascade by stimulating a repair response. Often this is accomplished by initiating an acute inflammatory reaction in the target tissue. This focuses the body's ability to heal itself by providing initial injury debridement through the action of macrophages and induces the proliferative phase of tissue repair, among many other key functions (24). This inflammatory phase lasts for 10 days. This is followed by the proliferative healing phase, lasting 30 days, and that involves chemical messengers released from the injury site that recruit fibroblasts to the injury site and induce angiogenesis at the site to facilitate tissue repair. The final phase of tissue healing is the remodeling phase, during which the rapidly laid down type 3 collagen fibers are gradually replaced by stronger, more organized type 1 collagen fibers (25). This remodeling takes up to 300 days to complete.

Successful regenerative medicine treatment depends not only on an accurate diagnosis but also in large part on precise guidance of injections. Many of the injectates used in regenerative medicine are costly to prepare or purchase and ultrasound-guided application, along with detailed knowledge of sonographic anatomy, is warranted (26). It is also difficult to assess the effectiveness of therapies without knowing precisely where they were placed in or near the injured tissue. In his 2013 review of palpation-guided versus ultrasound-guided peripheral injections, Hall showed a remarkably low level of accuracy when injections are performed based on palpation-guided landmarks (27). Soft tissue structures such as ligaments, tendons, joint capsules, and muscles, should be injected using real-time ultrasound guidance. Many spine targets have reasonable medical literature supporting the use of ultrasound guidance (28,29). Fluoroscopic guidance is suitable for intervertebral disc and transforaminal epidural injections, as well as for subchondral and intraosseous injections.

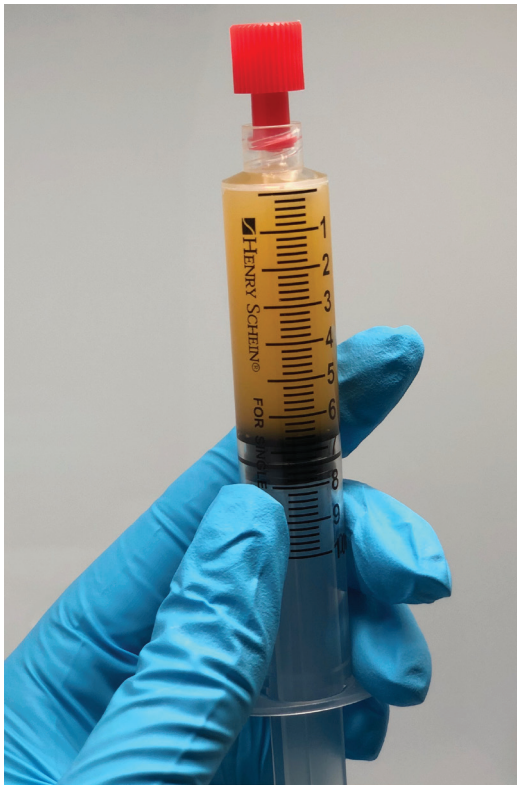
Prolotherapy

Prolotherapy, which is a contraction of the term "proliferative therapy," has been used as a treatment modality since the 1950s. From its conceptual organization and initial publication by Hackett (30), prolotherapy has targeted chronic ligamentous laxity as the etiology of many chronic cases of joint and spine pain. The theory underlying prolotherapy states that accumulated ligament laxity (through acute trauma or chronic repetitive actions) allows the joints and spine to move beyond their intended physiologic parameters. This disproportionate motion then leads to pathologic responses such as annular ligament tears resulting in vertebral disc bulges, or cartilage degradation and osteophyte generation resulting in osteoarthritis. In typical scenarios that produce chronic pain, this slowly progressive ligamentous laxity does not induce a productive healing response. Prolotherapy has generally been used as a regional modality, insofar as many ligaments work in concert to prevent abnormal joint motion. It is also used in tendinopathies (31).

The most studied "proliferant" solution is 15% dextrose, although other agents have been used. When injected in or very proximal to a ligament or tendon, the hypertonic dextrose induces mild cellular injury via a rapid osmotic shift of fluid, which in turn initiates an inflammatory response (32). This focused initiation of the healing cascade eventually will heal the previously unrecognized ligamentous injury and restore the damaged ligament to its ideal length and structure. By healing all or most of the major ligaments in a painful joint or section of spine, normal motion parameters will be restored, allowing the area to heal over time. Because the healing cascade is initiated by induction of inflammation, patients need to refrain from using anti-inflammatory medications for seven days prior to treatment and in the post-treatment recovery period. In the cases of depo preparations of corticosteroids, usage should cease 30 days before treatment as well as during the healing process in order to achieve optimal benefit from treatment.

For years the scientific evidence supporting the use of prolotherapy lagged behind its use in clinical practice. In the last decade, however, this lack of medical evidence has been effectively addressed by dedicated researchers. High-quality studies currently support the use of prolotherapy in many chronic injuries. One of the most significant of these studies was a multi-center RCT by Rabago, Patterson, and colleagues in which the investigators followed 90 patients for one year and concluded that prolotherapy resulted in clinically meaningful improvement of pain, function, and stiffness scores for knee osteoarthritis (OA) when compared to saline injections or at-home exercise programs. The protocol used in the study targeted both intra-articular and ligament structures around the knee (33). Hauser et al. published a systematic review of dextrose prolotherapy for chronic musculoskeletal pain. Their paper reviewed

14 RCTs and concluded the "use of dextrose prolotherapy is supported for treatment of tendinopathies, knee and finger joint OA, and spinal/pelvic pain due to ligament dysfunction" (34). Dumais and colleagues conducted a randomized crossover study for the treatment of knee osteoarthritis and concluded "the use of prolotherapy is associated with a marked reduction in symptoms, which was sustained for over 24 weeks" (35). A very interesting double-blind RCT conducted by Maniquis-Smigel and colleagues looked at the analgesic effect of a caudal epidural with 5% dextrose in water (D5W) in chronic low back pain. They concluded that "a caudal epidural with D5W for moderate-to-severe chronic non-surgical low back pain with radiation to either gluteal or leg areas demonstrated consistent analgesic responses and resulted in a long-term improvement in pain and disability" (36). There are now many high-quality statistically significant studies supporting the use of prolotherapy in chronic spine pain, joint osteoarthritis, and tendinopathies (37-41).



Platelet-rich plasma ready for use.

PRP

Platelet-rich plasma (PRP) is defined as a concentration of platelets above baseline. It has been widely accepted that a platelet concentration of four times baseline constitutes an adequate PRP preparation. However, that dogma is now being challenged, at least for some of the reasons enumerated below.

PRP therapy has been in clinical use since the 1990s (42). PRP is prepared from autologous blood by using centrifuge density-separation and removal of the red blood cells, and then further concentrating the platelet rich fraction of the remaining plasma. Platelets activate (degranulate) when they contact air, broken fragments of collagen (such as at the site of damaged tissue) or sense another platelet in proximity undergoing degranulation. When platelets degranulate they release alpha granules that contain up to hundreds of cytokines and chemical messengers that signal for inflammation and stimulate the body's endogenous repair mechanisms.

PRP has been shown to be an effective treatment modality in many well-done RCTs (43-48), although some of the evidence had shown mixed results (49). Laver et al. published a systematic review of the literature looking at 29 studies (11 RCTs) comparing PRP against hyaluronic acid (HA) for both knee and hip OA. They concluded that current clinical evidence supports the benefit of PRP treatment for knee and hip OA compared to several alternative treatments (51).

PRP has demonstrated clinical efficacy in the treatment of lumbar discogenic pain in an RCT with one-year follow-up (52). In addition, PRP has been shown to be effective in the treatment of low back pain due to sacroiliac joint dysfunction, lumbar facet syndrome, and low back pain associated with lumbar multifidus atrophy (53-55).

Sanchez and colleagues published a study showing the efficacy of treating severe knee OA utilizing intra-articular PRP in combination with sub-chondral injection of PRP at the medial femoral condyle and the medial tibia plateau (56). This study, as well as the previously mentioned study by Rabago, illustrate an emerging concept in regenerative treatments. In the past, osteoarthritis was treated with intra-articular injections only, regardless of the injectate (corticosteroids, hyaluronic acid products, PRP, etc). However, a more comprehensive model is emerging that includes treating pathologic joints by addressing at least two of the three components: 1) the intra-articular component (cartilage surfaces and synovium); 2) the soft tissue component (stabilizing ligaments and tendons); and 3) the sub-chondral osseous component, which is how the joint cartilage is both physically supported and nourished. Addressing at least two of the joint components is physiologically compelling and gaining support in the medical literature (57,58).

One issue that continues to confound the results of many RCTs comparing the tested substance to a saline-injected control is that there is reasonable evidence indicating that a saline injection is not a control but a treatment (59). Another confounding

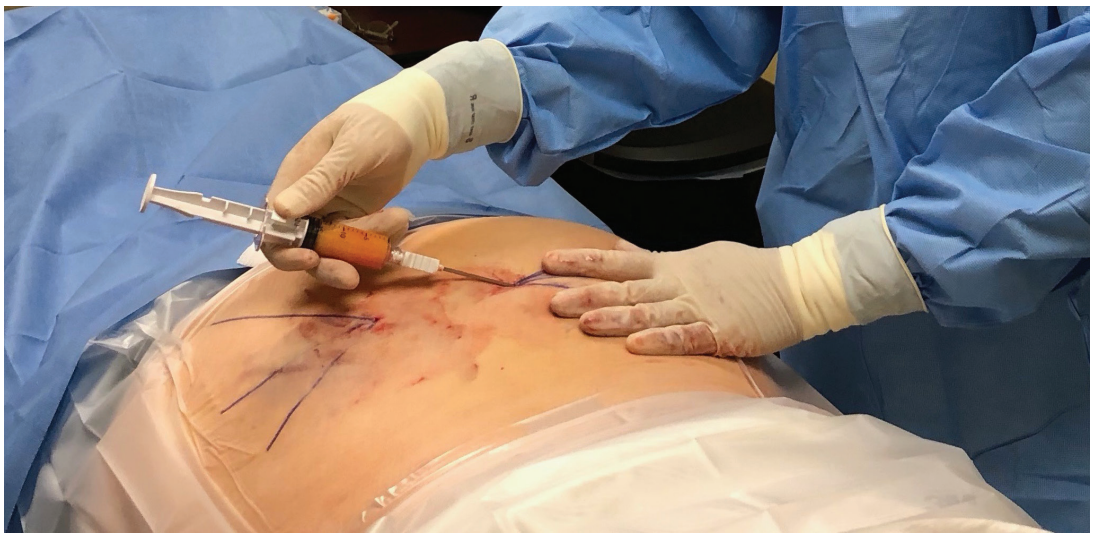
issue in PRP research may be attributed to the fact that it is difficult to statistically account for, and to appropriately power studies for, variations in even similar types of injuries, post-treatment recovery regimes, method of injection, skill of the clinician, and concomitant pharmaceutical use (and many other factors). Also, there is not one homologous preparation of PRP that is being compared in the literature (60). There are many commercially available systems and lab-based preparation protocols for the preparation of PRP. For example, there are leukocyte-rich and leukocyte-poor preparations, to name just one of the variables. Even if the method of PRP preparation is standardized, each individual patient starts with a different native baseline platelet count, resulting in a wide variety of final platelet concentrations within each PRP preparation, such that there is significant variability in the number of platelets per microliter injected even when employing the same preparation method. Furthermore, optimal platelet concentrations have not been established for musculoskeletal repair. A general rule is that 4-5 times concentration over baseline is a reasonable goal for a PRP preparation method. However, absolute platelet count per microliter is a more accurate method of comparison.

The qualitative differences in PRP also is a confounding variable in research. The presence and concentrations of the various blood components—RBCs, WBCs, and platelets—all have been proposed to have either beneficial or deleterious effects. For example, there is some data to support that leukocyte-poor PRP is more beneficial than leukocyte-rich PRP for intra-articular applications, while leukocyte-rich PRP may be superior for intra-tendon applications (61,62). Nonetheless, the clinical superiority of any one preparation has not been established in the medical literature and remains the subject of ongoing research (63). Few studies investigating the use of PRP actually document the qualitative nature of the PRP being injected. Mautner et al. gave us a comprehensive PRP nomenclature paper designed to define PRP based on the variable components to accurately and quickly describe the type of PRP being used in the prospective study (64).

Is PRP better than prolotherapy? There are only a few studies comparing the two modalities. In a double-blind RCT comparing 7 ml of intra-articular PRP and 7 ml of 25% dextrose, both groups had statistically significant improvement over six months. However, the PRP group was associated with greater improvement in their WOMAC scores (65). In a meta-analysis of 18 RCTs comparing injection therapies for the treatment of rotator cuff tendinopathy, both PRP and prolotherapy had statistically significant superiority over corticosteroids, NSAIDs, hyaluronic acid, and botulinum toxin at 24 weeks (66).

Autologous Mesenchymal Stem Cells

Autologous mesenchymal stems cells (MSCs) appear to facilitate musculoskeletal repair not so much by differentiating into the required target tissue but by binding to the injury site and acting in a paracrine fashion to facilitate tissue repair (67). Autologous stem cell preparations can be sourced from adipose derived MSCs and from bone marrow derived MSCs. Currently there is ongoing debate regarding which source is more optimal for musculoskeletal applications. Marrow-derived



Dr. Sean Mulvaney harvesting adipose as a source of mesenchymal stem cells.

stem cells have been shown to have a higher osteogenic and chondrogenic potential with in vitro studies. But human studies investigating the use of adipose-derived stem cells for the treatment of osteoarthritis have shown comparable results to those for marrow-derived treatments. Furthermore, adipose has a significantly greater number of stem cells than bone marrow per equivalent unit of measurement. In addition, as we age, the population of stem cells in the bone decreases precipitously while it remains relatively stable in the adipose. Finally, adipose-derived stem cells appear to maintain their regenerative properties more than bone marrow derived MSCs as we age (68). However, it remains to be seen whether any of these differences result in clinically meaningful differences in treatment outcomes insofar as both forms of treatment—adipose-derived and bone marrow-derived—appear to produce improved outcomes in human studies.

At the time of writing this, the U.S. Food and Drug Administration (FDA) is permitting bone marrow aspiration and centrifugation separation of bone marrow to density-select the nucleated cell layer and micro-fragmented adipose preparations. The FDA has not approved any technique that isolates the stromovascular fraction (SVF) from adipose tissue using enzymatic digestion of the extracellular matrix. Currently the FDA does not allow for culture expansion of harvested stem cells; this technique would exceed the FDA mandate of avoiding "more than minimal manipulation" of harvested autologous mesenchymal or hematopoietic stem cells. All preparations of autologous stem cells must be reinjected in the donor-patient on the same day as harvesting (69).

A review of the medical literature found six RCTs using bone marrow and adipose-derived stem cells to treat knee arthritis which concluded the following: there were no serious adverse events and there were superior radiological outcomes favoring stem cell injections. Two trials reported improved histological outcomes, improved arthroscopically-scored healing rates, and superior patient-reported outcomes. However, the level of evidence in some of the studies was reduced to level 3 due to perceived risk of bias (70). Emadenin et al. published a randomized, triple-blind, placebo-controlled trial using BMAC for knee OA of 43 patients and concluded that BMAC was safe and provided clinically significant relief of pain for over six months versus placebo (71).

Centeno and colleagues published a study of 840 OA knees with long-term follow-up treated with bone marrow derived stem cells and found this application to be both safe and efficacious (72). Centeno and colleagues also published a prospective multi-site study of 115 shoulder OA and rotator cuff tears treated with bone marrow derived stem cells which showed statistically significant improvement in DASH scores (73). Michalek and colleagues published a multi-center case control study of 1,114 patients with knee and hip OA treated with adipose-derived stem cells. At 12 months after treatment there was a 75% improvement in 63% of patients and at least a 50% score improvement in 91% of patients. There were no serious adverse effects associated with either the treatment or at the small volume adipose harvest sites (74). Hernigou et. al. recently published their landmark RCT comparing total knee arthroplasty (TKA) with subchondral bone marrow injections for severe knee OA, with a 12-year follow-up. Both groups had similar favorable improvement. The cell therapy group showed improvement in both cartilage and bone marrow lesions. There were significantly greater medical and surgical complications following TKA compared to the cell injection group (75). Hernigou and colleagues also pioneered the technique of a BMAC treatment for avascular necrosis (AVN). Using percutaneous injections into the necrotic area of femoral heads, they demonstrated both safety and clinical efficacy for this condition which is otherwise treated with hip core decompression and eventually total hip arthroplasty (76,77). Pettine and colleagues published a study with 3-year follow-up which showed safety and significant efficacy using BMAC injections in lumbar intervertebral discs with symptomatic annular tears to treat lumbar discogenic pain with a VAS improvement of 71% and an ODI improvement of greater than 64% (78). Hernigou also published a landmark rotator cuff repair study with 10-year follow-up comparing surgically repaired rotator cuff tears with and without BMC augmentation. In the BMAC augmented rotator cuff repairs BMAC was surgically placed in the repair site as well as the subchondral foot print of the rotator cuff repair site. There were 45 patients in each group. At six months 100% of the BMC augmented repairs showed MRI and U/S evidence of healing, whereas the repair-only group showed 67% healing. At 10-year follow-up, the BMC augmented group showed 84% were still healed versus only 44% of the repair-only group (79). Gobbi et al., in his landmark work on osteochondral defect repair in the knee, prospectively treated 15 patients with large

chondral defects with a type I/III collagen matrix seeded with autologous BMC and sealed with fibrin glue as a single stage dry arthroscopic procedure. This resulted in significant improvement in patient outcome scores, MRI evidence of healing, and second look arthroscopy showing normal to near normal hyaline like cartilage in over 80% of the subjects (80).

Russo and colleagues published a retrospective observational study of 30 patients treated with autologous micro-fractured adipose for knee OA. They concluded the treatment was successful, with significant improvement in VAS, KOOS, and IKDC scores, and that it was both safe and compliant with current regulations (81). Striano and colleagues published a case series of 18 shoulders with OA and or rotator cuff tears treated with micro-fragmented adipose and concluded, after a one-year follow-up, that there was significant improvements in pain, function, and quality of life (82). Although there is ongoing debate about which source of MSCs is superior for orthopedic regenerative applications, both need further high quality RCT level evidence to support their clinical efficacy.

The Australasian College of Sports Physicians published a position statement in 2015 stating that autologous MSC stem cell therapy should have the same 4 phase trial safety testing as a new drug before being considered safe. This seems to be an onerous standard for a person's own, non-culture expanded cells. However their position statement was also covering potential use of culture expanded MSCs (83). Nonetheless, currently there are no reports of non-expanded or culture expanded MSCs having tumorigenic potential (84). Regarding the safety of non-culture expanded MSCs from either bone marrow or adipose tissue, current medical literature supports that both sources appear to be safe and reasonably efficacious for the treatment of knee and hip osteoarthritis and some tendinopathies and tendon tears; however more high-quality research is needed.

Alpha-2 Macroglobulin

Alpha-2 macroglobin (A2M) is a serum protease inhibitor. It is a complex molecule that sequesters and neutralizes catabolic mediators. It is found in the blood and soft tissues but it is not significantly present in joint fluid (85). A2M can be concentrated from a patient's blood and injected into an injury site. The theory and goal is to reduce the catabolic milieu around an injury location or the intra-articular environment of arthritic joints. There is only one low-level study currently supporting its clinical use. However, there is an interesting animal study by Wang and colleagues which illustrates that A2M may have utility in ameliorating the post-traumatic arthritis associated with anterior cruciate ligament (ACL) rupture. In the event of an ACL rupture, there is an extreme intra-articular catabolic event that has been shown to induce chondrocyte apoptosis and eventual post-traumatic arthritis, even if the ACL is surgically reconstructed (86). In Wang's study, an ACL injury was induced in 60 rats, 30 of which received A2M injections, while a control group received saline injections. The A2M group did not go on to develop post-traumatic arthritis, while the saline group did. Wang concluded that "A2M is a powerful inhibitor of many cartilage catabolic factors and that it can attenuate posttraumatic OA cartilage degeneration" (87). Although making treatment decisions based on animal studies is sub-optimal, there is not a currently accepted treatment for reducing the post-traumatic arthritis seen in ACL injuries. A2M is an autologous and safe option which may prove to have significant clinical utility in reducing the development of post-traumatic arthritis in the setting of intra-articular trauma.

Other Human Tissue-Derived Allograft Products

Allograft products used in regenerative medicine consist of donated human placental and amniotic tissue derived allografts and components of umbilical cord blood mesenchymal stem cells, including the isolated exosomes of these cells. These products do not contain viable MSCs. Although these products have a few clinical level-4 studies published which show initial safety and potential use for musculoskeletal injuries, overall, they lack the published medical evidence to demonstrate efficacy (88-91), and they are generally expensive to administer. Allograft products may be a reasonable option, especially for patients with contraindications to other regenerative autologous options, such as a of history blood or bone marrow cancers.

Conclusions

Regenerative medicine treatments for chronic musculoskeletal conditions have a growing body of medical evidence supporting both their safety and their efficacy in clinical application in joints, spine, ligaments, tendons and vertebral discs. Prolotherapy and PRP have reasonable RCT level clinical evidence supporting their safety and efficacy. Autologous non-culture

expanded mesenchymal stem cells, whether adipose or bone marrow derived, appear to be safe, and the initial body of medical evidence show promise as a therapy to improve pain and function in chronic musculoskeletal maladies. Allograft regenerative medicine products have only few level-4 clinical studies supporting their clinical application and require more unbiased published literature to make any recommendation on their use. The term "regenerative medicine" may imply true tissue regeneration, but this has not been validated in the literature. Instead, the term regenerative medicine can be associated with enhancement (through relative reduction of catabolic factors) or activation of endogenous healing mechanisms. The efficacy and safety of regenerative medicine techniques should be thoughtfully balanced against the same considerations when employing many currently accepted therapies, including both surgical and non-surgical options. There is real, quantifiable mortality associated with arthroplasty (5,000 deaths per year in the U.S. alone) (92) and significant morbidity associated with NSAID and corticosteroid use. In similar medical literature reviews, it is both common and academically prudent to comment that "further high-quality research is needed." While this is certainly a true statement, there is enough medical evidence to both critically re-evaluate many currently accepted therapies and consider some regenerative options to help both reduce pain and return patients to movement.

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Identification of Risk Factors and Prevention of Injury in the Older Runner

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Introduction

Running has been associated with a reduced incidence of morbidity and mortality of multiple chronic diseases that commonly affect the older population. Due to its benefits, there has been an increase in the number of older people who elect to participate in recreational and competitive running to maintain or improve their health and physical fitness (1). Despite these health benefits, concerns about the high incidence of predominantly lower limb musculoskeletal injuries have been raised. The incidence rate for running-related lesions in the musculoskeletal system is as high as 92.4%, or 6.8–59 injuries per 1,000 hours of exposure to running (2).

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Considering the high risk for injury, multiple interventions have been suggested as methods to reduce the frequency and/or severity of lesions. Prevention strategies can be classified as primary, secondary, and tertiary. Primary prevention aims to prevent disease or injury before it occurs. Secondary prevention strategies try to reduce the recurrence of an established injury; most prevention occurs at this level. Tertiary prevention aims to reduce the impact of long-term sequelae of an injury. The current medical literature mainly evaluates primary and secondary injury prevention and limited scientific information is available on the older runner (3).

Van Mechelen et al. proposed a four-step model with the objective of providing an effective approach to preventing sports injuries. The model suggests identification and description of the injury (incidence and severity) as a first step. Secondly, the aetiology and mechanisms of the injury need to be recognized to determine predisposing factors that make a runner susceptible to injury. Identification of such factors contributes to the development of injury prevention strategies that are likely to reduce the risk and/or severity of injuries. Finally, the effectiveness of the strategies needs to be evaluated and proven (4,5).

For the purpose of this article, the older runner will be defined as an active individual ≥50 years of age who participates in recreational or competitive running or runs for health maintenance (6).

Epidemiology

It is expected that approximately 56% of recreational runners and as high as 90% of runners training for a marathon will sustain a running-related injury each year. Eighty percent of running disorders are overuse injuries, the knee being the predominant site of injury with an incidence ranging from 7.2% to 50.0%. Less commonly injured sites are the ankle, hip/pelvis/groin, and lower back, ranging from 3.9% to

16.6%, 3.3% to 11.5%, and 5.3% to 19.1 respectively (7). Recent studies have observed an association between age and an increased risk of developing a running-related overuse injury, especially in those over the age of 45 years presumably because of reduced muscle strength, flexibility, and altered gait biomechanics. Devita et al. observed that the older runner had a higher incidence of soft tissue-type injuries to the calf, Achilles tendon, and hamstrings when compared to their younger counterpart (8).

Identification of Risk Factors

Risk factors for lower extremity injuries in runners are attributed to a combination of factors that can be categorized as intrinsic (e.g., malalignment and muscle weakness), extrinsic (e.g., training errors and inappropriate equipment), modifiable (e.g., BMI, level of activity, and weakness), and non-modifiable (e.g., age, sex, and previous injury).

Training mileage and a history of a previous lower extremity injury are two risk factors consistently identified as significant predictors for running-related injuries (9). Macera et al. reported that among runners with a history of a lower extremity injury in the 12 months prior to a road race, the risk of subsequent injury in the month after the race was 6.3 to 7.6 times higher than for runners without a previous injury (10). Hootman et al. suggest that running at a pace slower than 15 min/mile may be protective of lower extremity injury among recreational adult runners (9). One high-quality study observed that running injuries were higher among men who had participated in more than six races in the last year (7). Fredericson et al. stated that sudden increase in running mileage, change in training volume or intensity, and crossing a threshold of 40 miles/week were all high risk for injury (11). Yeung et al. observed that training at a distance of 0-40 km/week was protective against the occurrence of calf injuries and that those who trained 1-3 days a week were less likely to be injured than those training 5 days a week (12). Soligard et al. recommends that athletes should limit weekly increases of training load to <10% to ensure adequate adaptation and reduced risk of injuries (13).

Since running injuries are considered to arise secondary to the summation of several factors, modifying one risk factor will not likely lead to a decrease in the number of running-related injuries. For this, a multifactorial prevention program is recommended to assure more effective means of treating a lesion.

Components of a Prevention Program

Understanding the epidemiology, mechanics, and risk factors associated to running injuries in the older athlete is necessary to develop adequate injury prevention programs. A multicomponent approach directed towards specific etiological and modifiable risk factors is encouraged. Since each person's body responds differently to the stress caused by running, individualized training programs are advised.

Table 1.
Predisposing Factors for Overuse Running Injuries in the Older Runner

Intrinsic Factors	Extrinsic Factors
Malalignment (e.g., pes planus, pes cavus, rearfoot varus) *	Body composition
Previous injury*	Training errors (e.g., excessive volume, excessive intensity, faulty technique)
Muscle imbalance	Surfaces (e.g., hard, soft)
Muscle weakness	Shoes
Age*	Equipment
Sex*	Environmental conditions (e.g., hot, cold, humid)
Genetic constitution*	Psychological stressors
Body size	Inadequate nutrition

**Non-modifiable risk factors; Modified from Paluska (20)*

Table 2.
Prevention Strategies for the Older Runner

Primary Prevention Goal: Prevent disease or injury before it occurs	**Secondary Prevention** Goal: Reduce the recurrence of an established injury	**Tertiary prevention** Goal: Reduce the impact of an injury's long-term sequel

Intervention:
• Maintain adequate weight/BMI
• Incorporate into running regimen exercises to improve:
  ◦ strength
  ◦ endurance
  ◦ flexibility
  ◦ balance-coordination
• Running should not exceed >40 miles/week
• Use of proper equipment
  ◦ avoid use of worn out shoes
	Intervention:
	• Rest from running
	  ◦ cross training
	  ◦ low weight bearing exercises
	• Maintain running frequency, duration, and distance below injury level
	• Correct errors in running technique
	  ◦ forefoot
	  ◦ increasing step rate by 10%
	• Strengthening exercises to correct muscle imbalances/ weakness
	• Continue flexibility/balance-coordination exercises
	• Knee brace for anterior knee pain
		Intervention:
		• Weight loss
		• Continue exercise program
		• Modify residual biomechanical or functional deficits
		• Mileage kept under symptomatic level
		  ◦ limit weekly increase of training load to <10%

Stretching and Strengthening Exercises

Static stretching has been shown to improve flexibility, but there is currently insufficient evidence to support that such intervention is effective in preventing lower limb injuries. Pope et al. observed that stretching (e.g., static stretching of the iliopsoas, quadriceps, hamstrings, soleus, and gastrocnemius muscles for 20 sec.) before exercise did not produce a statistically significant reduction in the risk of soft tissue injuries (14). Van Mechelen et al. described a protocol that included a warm-up of 6 min. of running exercises, 3 min. of loosening exercises, and 10 min. of stretching exercises to major lower-limb muscles (3 x 10 sec. static stretches); however, the evaluation of this intervention did not demonstrate that a warm-up and stretching session prevented running-related injuries (4). Current literature is inconclusive in determining if dynamic stretching is successful in decreasing risk for sports related injuries. Despite such findings, consensus among sports medicine practitioners still leans in favor of stretching by incorporating flexibility exercises composed of dynamic exercise through a sport's specific active range of motion prior to activity and static stretching to help increase muscle and tendon length following running (15).

Research has shown that power training with heavy weights (improves power) or plyometric exercises (improves speed) can augment running economy and endurance performance. An increase in strength and running economy can improve mechanical efficiency, muscle coordination, and motor recruitment patterns, and thus may contribute to decreasing incidence of overuse injuries in runners (16,17).

A study by Turner et al. included a regimen of plyometric training 3 times a week for 6 weeks in addition to the subject's established running regimen. The plyometric training involved six exercises performed as follows: warm-up with submaximal double-leg vertical jumps, double-leg vertical power jumps, single-leg vertical power jumps with double-leg landing, submaximal double-leg vertical springing jumps, maximal split-squat jumps, and submaximal double-leg springing jumps on an incline. The 6-week program of plyometric training added to regular distance running training improved the running economy of the participants (16).

Johnston et al. included a resistance-training program performed 3 days a week for 10 weeks. Subjects continued running 4-5 days a week for 20-30 miles each week and incorporated strength-

training exercises with free weights to their regimen. Exercises included parallel squats, seated press, bench press, bent leg heel raise, knee flexion, hammer curl, and weighted sit-ups. There was evidence of a 4% improvement in running economy and a significant increase in strength (17).

Since running involves multiple eccentric contractions, it is recommended that resistance and plyometric exercises be aimed at improving eccentric strength to help in decreasing lower extremity injuries (15,18). The scientific literature postulates that running strengthens the hamstrings and calf muscles more than muscles located in the anterior leg and that such muscle imbalance increases the risk of overuse injuries. To correct such imbalance, exercises that target the weaker muscle groups should be addressed during strengthening exercises (4).

Balance and coordination exercises should also be emphasized as they help in preventing acute injuries in the older athletes by improving movement control and decreasing the risk for falls (19). Training programs for older runners should progress gradually in terms of intensity, volume, and pace and should be individualized based on gender, health conditions, and running experience (18,20).

Education and Modification in Biomechanics

Education should target a change in running behavior by reducing the running frequency, duration, and distance below injury level (15). The athlete must be made aware of the importance of targeting an ideal body weight to avoid excessive peak forces on weight bearing structures during running, which may predispose to overuse injuries (20). Zheng et al. showed that overweight and obese patients demonstrated a higher risk of knee osteoarthritis (OA) (2.45 and 4.55, respectively), and that the risk of knee OA increased by 35% with every 5 kg/m2 increase in BMI (21). The athlete must be educated on the importance of avoiding sports activities such as running until he/she is free from pain and range of motion and muscle strength have returned to pre-injury level. Once the athlete is ready to return to running, it is crucial to instruct them to limit weekly increases of training load to <10% as a means to avoid re-injury (13).

Studies have shown that modifications in running technique (increase in step rate, decrease in step length, and mid- or forefoot running) can be effective in reducing knee and hip joint loads, as well as vertical ground reaction forces. Increasing the athletes step rate by 10% or greater with a proportional decrease in step length diminishes the impact load and may reduce the risk of developing a running-related injury, as well as help in recovery from an existing injury. Heiderscheit et al. describes that by running with an increased step rate, the reduction in energy absorption at the hip and knee may help those with injuries in such joints and associated tissues (22). Bus et al. postulated that running at lower speeds reduced impact on the body and aided in compensating for the reduction of the shock-absorbing capacity in the older runner (23).

Increasing the athletes step rate by 10% or greater with a proportional decrease in step length diminishes the impact load and may reduce the risk of developing a running-related injury, as well as help in recovery from an existing injury.

The current medical literature demonstrates that changing the running technique on selected injured runners (e.g., patellofemoral pain (PFP) syndrome and OA) is an option to reduce recurrent injury or disease progression. Esculier et al. observed that by increasing step frequency and modifying footstrike pattern to midfoot or forefoot, runners with PFP syndrome demonstrate a significant improvement in pain and function (24). On the other hand, there is no definite evidence that changing the running gait from rearfoot to mid- or forefoot strike necessarily benefits all runners, especially those that have no running-related injuries (25).

Equipment

Yeung et al. suggests that wearing a patellofemoral brace appears to be effective for preventing

anterior knee pain (12). Studies have demonstrated that wearing orthotics or using shoe inserts does not seem to be useful for compensating for biomechanical deficiencies and has no effect on injury prevention. Fokkema et al. recommends that if a runner uses a certain type of shoe (neutral, cushioned, stability or motion control shoes) and does not have an injury, he/she should avoid changing shoe type (26). Recent studies have concluded that wearing worn-out shoes increases the risk of injuries and that no particular shoe has a preventive advantage over other brand names (4,26). Yeung et al. found no evidence to suggest that using a prescription running shoe based on foot shape reduced the rate of lower limb soft tissues injuries when compared to regular running shoes. There is no evidence that polyester socks or wearing double socks reduces lower limb overuse injuries (12).

Running surfaces

The current literature has been unable to find an association between different running surfaces (asphalt, concrete, grass, and track) and running injuries. Tillman et al. described that runners are capable of adjusting their limb stiffness and movement patterns depending on the hardness of the running surface while maintaining a constant stride frequency, ground contact time, and peak ground reaction forces. In turn, if the runner is unable to make rapid adjustments in their running mechanics to adapt to the surface stiffness, this may eventually lead to injury (27).

Outcome Measures

A limited number of studies have looked at how establishing a preventive training program reduces the risk of initial and recurrent injuries in the older runner but studies evaluating young runners have demonstrated positive outcomes with modifications in training (11,14,24).

Esculier et al. demonstrated that through a training program that consisted in landing pattern modifications (shortening stride length and avoiding a rearfoot strike landing), participants with PFP syndrome experienced reductions in loading rates and pain scores (24). Fredericson et al. observed that long distance runners with iliotibial band syndrome that completed a 6-week rehabilitation program focused on correcting strength deficits in the hip abductors, were pain free and able to return to running with no recurrence at a six-month follow-up (11). Yeung et al. described that runners who train 15–30 min. a day, 1-3 days a week as compared to those who train 45 min. a day, 5 days a week in a 12-week period (82 km compared to 280 km) show a significant reduction in lower extremity overuse injuries (14).

Summary

- Although running has multiple health benefits for the older runner, there is a high rate of running-related musculoskeletal injuries.
- The four-step model is an effective approach to preventing running injuries in the older runner: 1) identification and description of the injury 2) identifying the aetiology and mechanisms of the injury 3) introducing preventive measures 4) assessing the effectiveness of the preventive measures.
- Effective prevention strategies in older runner include altering modifiable risk factors such as training volume, muscle weakness, and improper equipment. As for altering running biomechanics, recommendations are mixed in the literature: 1) the older runner with a running-related injury (e.g., PFP and OA) benefits from a trial in altering footstrike pattern to mid- or forefoot 2) there is no evidence to suggest change in running technique for the older runner who has not been injured.
- Further research is needed to evaluate outcome measures of interventions implemented to reduce the risk of running-related injuries in the older runner.

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IIRM NEWS

(continued from page 2)

Association of International Marathons and Distance Races (AIMS)

In September, IIRM Executive Director Chris Troyanos, ATC, traveled to Tallinn, Estonia for the 2018 AIMS World Congress where over 250 leaders in marathons and road races attended. As part of a partnership agreement, the IIRM is committed to provide a medical lecture at each of AIMS' annual congresses with representation from our leadership or membership base. This year, Chris spoke on the impact global weather changes have on endurance events.

Road Race Management

The IIRM had a presence at the Road Race Management Race Directors' Meeting held in November in St. Petersburg, Florida. Chris Troyanos, ATC, presented on, frequency and treatment of running injuries at road races. According to Chris, "It was a great trip that forged many new relationships and helped to move the needle forward as we strive to educate those that manage races and their runners."

IAAF

The IIRM is in the process of forming an important partnership with the International Association of Athletics Federation (IAAF). The goal is to have the two organizations collaborate on the development of medical guidelines for all IAAF events, including road races and track and field events. We will also be working together to expand the IIRM's continuing education activities to Europe.

If you have any questions or comments, we'd love to hear from you. Please write to the IIRM at journal@racemedicine.org.

The WBGT Index: A Primer for Road Race Medicine

Samuel N. Cheuvront, PhD, RD, FACSM and Yuri Hosokawa, PhD, ATC

The mission of the International Institute for Race Medicine (IIRM) is to promote the health and safety of athletes participating in endurance events through education, research, and the development of medical best practices. This primer is written in support of the IIRM mission and describes the basic science and practice of using the wet bulb globe temperature (WBGT) index to aid in mitigating the risk of exertional heat illnesses.

What is the WBGT Index?

High air temperature, high humidity, thermal radiation, and low air movement are causes of environmental heat stress. The WBGT index encompasses all of these environmental causes of heat stress into one number that is used to characterize the potential effects of hot environments on runners. Figure 1 illustrates the three WBGT components and the formula for calculation. A traditional WBGT apparatus measures air temperature from a shaded dry bulb thermometer (Tdb). The contribution of humidity is determined from a wet bulb temperature (Twb), which is measured by covering a thermometer bulb with a wet wick. Radiant heat (solar load) is assessed by a black globe thermometer (Tbg) which consists of a 6-inch hollow copper sphere, painted matte black on the outside, and containing a thermometer at the center of the sphere. The traditional WBGT apparatus is comprised of non-standard instruments that can be cumbersome to use and maintain. However, comparable results (1) can now be obtained with several modern and highly automated WBGT monitoring systems that use smaller diameter black globes, waterless wet bulb temperatures, or other advances that afford miniaturization and improved portability. The reader interested in the history and many detailed assumptions and limitations of using the WBGT index should consult Budd (2).

The Importance of All Three WBGT Components

When runners start a race they instantly begin using energy at a rate that is 5 to 10 times greater (or more!) than resting metabolism (1 MET). However, only 20% (or less) of the energy is used for work—the rest is converted to heat. The metabolic heat

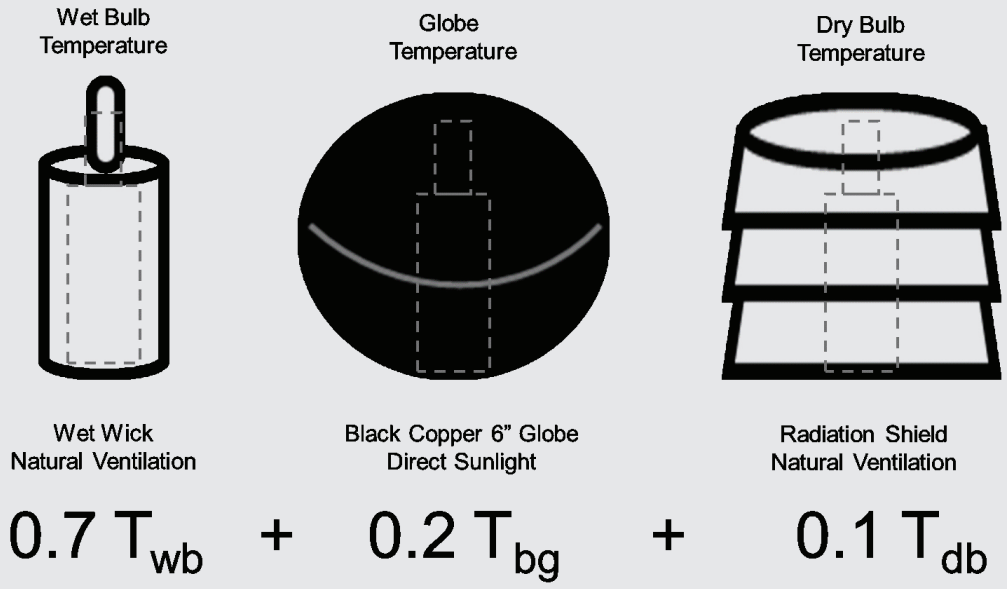

Figure 1.
WBGT index components and formula.
Dashed line image represents a standard thermometer within each component.

being generated by runners is the principal reason for increases in blood flow and sweating, referred to as exercise thermoregulation. Specifically, increased blood flow to the skin produces dry heat loss (radiation and convection) and the evaporation of sweat secreted on the skin surface produces evaporative heat loss.

The effects of the environment on heat balance are normally indirect; that is, the environment affects how much body heat can be lost by dry or evaporative means, rather than contributing directly to heat gain (with exceptions). A runner's skin is normally warmer than the surrounding air, which allows for heat loss from body to environment; however, when the Tdb is > 36^0 (97^0F), hot air causes dry heat gain. The Tdb represents 10% of the WBGT index. The Tbg is lower than Tdb at night and similar before sunrise and after sunset, but otherwise variable based on cloud cover and time of year. In mid-morning and early afternoon on a cloudless summer day, the Tbg can be 1.5 to 2.0 times higher than Tdb. Furthermore, the solar load on the body can equal 2 METS, which would increase body heat storage similarly to running 30 seconds faster per mile! The Tbg represents 20% of the WBGT index. Significant sweating can occur even in cool environments because, as mentioned above, metabolism is the primary driving force behind body heat production. Cool skin will reduce sweating in proportion to larger dry heat losses (by radiation and convection), but as Tdb increases the dependence of sweat evaporation for body cooling becomes paramount. In warm and hot environments, sweat evaporation can provide all the cooling necessary, if the air is dry. But when the Tdb approaches skin temperature and the air is also humid, the water vapor pressure in the air can become higher than it is for sweat on the skin, thus preventing evaporation. For this reason, Twb represents 70% of the WBGT index as saturation of air dictates the upper limit for heat dissipation when the air is warm or hot. Lastly, high air flow will reduce the WBGT index by altering the rate of convective and evaporative heat loss, but this is a smaller concern for runners who generate their own air flow equivalent to running velocity. The absolute contribution that each component contributes to the overall WBGT naturally depends on the prevailing weather. Figure 2 provides one example.

The solar load on the body can equal 2 METS, which would increase body heat storage similarly to running 30 seconds faster per mile!

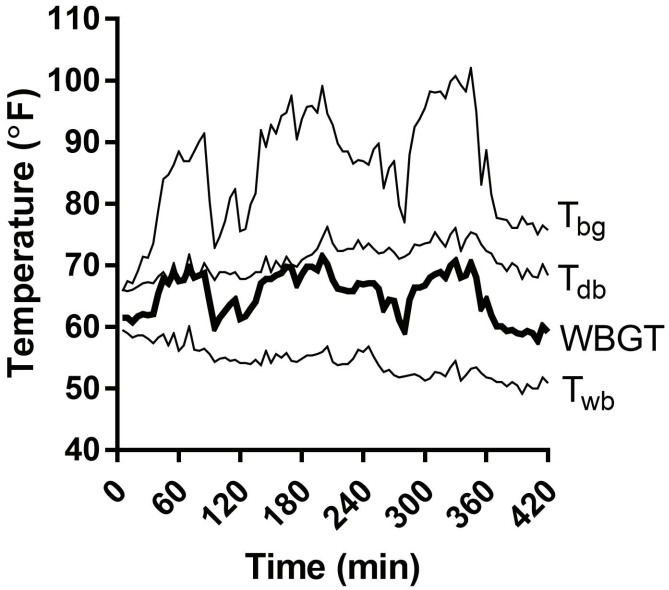

Figure 2.
The WBGT and components measured on-site at five minute intervals for seven hours during the 2017 Boston Marathon. Fluctuations between green and yellow flag categories this day were driven principally by changes in cloud cover which produced spikes in the black globe temperature. *(Unpublished report from S. Cheuvront to the Boston Athletic Association, April 26, 2017).*

Table 1.
Generalized heat stress flag color warnings for runners based on the Wet Bulb Globe Temperature (WBGT) index.[1]

Flag Color	WBGT, °C (°F)	Risk for Hyperthermia	Warning
WHITE	< 10 (< 50)	Low but possible risk for hypothermia	Wind, rain, longer races, and slower pace increase risk
GREEN	< 18 (< 64)	Low	Remain alert as exertional heat illness may still occur
YELLOW[2]	18-23 (65-73)	Moderate	Caution and slower pace[3] recommended
RED	23-28 (73-82)	High	Extreme caution and slower pace[3] strongly recommended
BLACK	> 28 (> 82)	Extremely High	Race cancellation or non-participation recommended

1 Adapted from Hughson et al. (1983) and ACSM (1987)
2 Sometimes referred to as AMBER
3 Performance impairments make personal best (PB) performances very unlikely and attempts to PB increase exertional heat illness risk significantly; see also Table 2

WBGT Index Flag Categories

The WBGT is used to manage the risk of exertional heat illness using color-coded heat stress flag categories. The development and first formal recommendation for using WBGT categories for road race risk management, as defined and described in Table 1, was by Hughson et al. in 1983 (3). The American College of Sports Medicine adopted the recommendations in their 1987 position stand on the prevention of thermal injuries during distance running (4) and continues to advocate for the same today. Table 2 provides important running performance information not normally considered in the discussion of WBGT and exertional heat illness risk management. It is important to teach runners that heat stress impairs performance before it increases the risk of exertional heat illness. A slower pace is recommended to reduce risk when the WBGT reaches yellow and red flag status (Table 1). Runners determined to attempt a personal best in those conditions are unlikely to succeed but will significantly increase their risk of illness. As pointed out above, a fast pace has the single greatest influence on body heat storage.

WBGT Measurement and Forecasts

Traditional WBGT thermometers (e.g., military) are suspended in the sun at a height of 4 feet above the ground and a period of 20 minutes is allowed

Table 2.
Distance-specific WBGT index thresholds for impaired running performance are lower than those for exertional heat illness risk.

Race Distance (km)	Exertional Heat Illness Risk (°C/°F)	Performance Impairment (°C/°F)
5	> 29 / 84	> 25 / 77
10	> 28 / 82	> 20 / 68
42	> 21 / 70	> 15 / 59

Data compiled from McCann and Adams (5), Ely et al. (6), and Roberts (7).

(photo by S. Cheuvront).

Figure 3.
WBGT index measurement made on-site using a sample portable WBGT system. (Runners in Newton, Massachusettes, at the 30 km mark of the 2013 Boston Marathon.)

to elapse before readings are taken. Modern 'all-in-one' WBGT instruments should be placed on a tripod 4 feet (1.2 m) above the ground and a similar warm-up period allowed before making a first measurement. The WBGT index is best measured on location (Figure 3) or as close as possible to the location of interest in real time (8). This can be a challenge for road races that span 5 to 42 km.

As a replacement for on-site WBGT instruments, various WBGT estimation models have also been proposed that utilize conventional measurements taken at local weather stations such as air temperature, relative humidity, solar radiation, and wind speed (9). For example, a formula developed by the Australian Bureau of Meteorology (ABM) requires just the air temperature and relative humidity for estimating the WBGT. This makes the formula a field-friendly solution since the air temperature and humidity data can be easily obtained via weather forecasts, meteorological updates, or with relatively inexpensive devices. However, the formula is not sensitive to the change in the amount of solar radiation (e.g., Figure 2) and wind currents at a given combination of air temperature and humidity, which limits its accuracy and usefulness as described above. Another tool that is commonly used by researchers is called the Liljegren model, which estimates WBGT using air temperature, relative humidity, solar radiation and wind speed. Because the components of the Liljegren model closely align with the traditional WBGT, it has been shown to produce WBGT estimates that are close to the actual WBGT values (9). Nevertheless, the distance from the weather station and other factors can still influence the accuracy of the estimated values.

WBGT forecasting may become possible if the spatial accuracy needed to calculate a WBGT estimate that is close (enough) to the actual WBGT is determined. However, since every location has its own unique geographical and climate characteristics, use of off-site data requires special considerations. For any race directors that are considering the use of off-site data to estimate local WBGT, it is highly recommended to monitor and compare the on-site course measurements with the weather station data in advance of the race to determine its accuracy (8).

Summary

Maintenance of thermoregulation is vital to sustaining health and optimizing running performance in the heat. The WBGT is an objective measure that can inform race participants about the environmental allowance under which they can safely run in warm conditions. Race directors should consider using one of many 21st century devices for measuring on-site WBGT (1,8) and implementing the flag notification system to systematically address the risk of heat stress. Effective use of WBGT alerts can help modify runners' behaviors as environmental heat hazards become imminent.

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Visit the IIRM blog, authored by Marine Corps Marathon Medical Coordinator Michele "Shelly" Weinstein, PT, MS, SCS, ATC, USN Retired. Shelly is also co-owner of Cogent Steps, LLC (medical education and emergency management education), an emergency response instructor for the American Physical Therapy Association's Sports Section, and faculty member of the US Navy Sports Physical Therapy Residency. Among the topics discussed in the blog are testing and treatment of hyponatremia, youth and long distance running, race participation of athletes with disabilities, the cost of managing safety for events, and making sense of the supplies list for the endurance event medical tent. To view or contribute to the blog, go to https://racemedicine.blogspot.com. We welcome your contributions!

Space Blankets: Heat, Help or Hype?

Dr. Lowell Greib, MSc, ND, CISSN

With a sea of slow moving, heavy breathing, and salt stained hobbling bodies, one may think they have entered a zombie apocalypse. However, this real life scene of "The Walking Dead" is something that all medical directors have experienced. As these half lifeless bodies slowly move through our finishing shoots, they drag themselves toward a glimmer of hope, draped in mass and hanging over tables. The shine of space blankets infuses these creatures with an essence of revitalization and the magical return of their vigor. But do these long-used aids actually help runners as they try to brew life back into themselves?

Endurance sport occurs in a variety of thermal conditions that can range from hot and humid to cold and dry, with every permutation imaginable in between. Race directors, and by extension, medical directors attempt to equip themselves with processes and tools that offer a positive race experience to a participant while concurrently mitigating health risks. Over the years the cultural norm, particularly in endurance road races, of receiving a reflective blanket has been a tool to help mitigate excessive cooling in cold temperatures and overheating in sunny, hot climates.

With claims of reflecting up to 90% of a person's body heat and can be flipped to deflect external heat sources (1), it appears to be an easy choice when implementing a risk reduction strategy into a race environment.

As a medical director, it is important to establish runner safety protocols and best practices shown in science and published literature. These are the foundations of ensuring the safety of runners in any race. As such, an extensive literature search was completed to identify if the implementation of reflective blankets in a setting such as a marathon is founded. What was surprising is that there is virtually nothing published showing use in a sporting environment. Virtually all of the current literature documents efficacy of reflective blanket for use in the peri-, intra-, or post-operative environment.

Photo Credit: MarathonFoto

Photo Credit: MarathonFoto

One literature review (2) on 'space blankets' yields an interesting history. During the space race of the 1960s, the space research organizations were looking to design a flexible 'super insulator.' Not long after, the heat reflective properties of these flexible and compact sheets were used for survival purposes. The reflective properties of a space blanket can, in theory, work on the radiated energy emitted from the athlete.

As endurance athletes compete, they metabolize substrate and produce energy. This kinetic energy is what propels the runner through muscle contraction during the event. Humans, as we know, are very inefficient—as upward of 75% of this kinetic energy is lost as thermal energy (3). During an event, effective heat dissipation is key in maintaining an appropriate core temperature in an athlete. There are two primary classes of heat loss in an athlete: wet and dry. Wet heat loss is due to the evaporative effect of sweat. It is the primary thermoregulation mechanism of the body and is effective in dissipating heat production during metabolism. It can account for up to 50% of heat dissipation (4). The remainder of the thermoregulatory effects are as a result of 'dry cooling,' which is the summation of the convective and radiant heat dissipation effects.

Upon reflection of the primary literature search completed, it is now more understandable why reflective blankets are used in controlled operative environments. There is mitigation of evaporative effects and controls can be made for convective effects (i.e. the patient is stationary and can be wrapped). However, in a race environment, can reflective blankets help warm a runner? Literature yields zero data. Speculatively, based on human physiology and science, one would think that the warming effect would be minimal for the following reasons:

1. Runners are still sweating when crossing the finish line, maintaining a significant evaporative cooling effect.
2. Runners are typically still moving while wearing the reflective blankets which increases the convective cooling effect.
3. Runners are NOT fully wrapping themselves and this decreases the efficacy of the reflective properties of the blanket. The blanket is often tied like a super hero cape.
4. Runners may not wear the blanket with the reflective side inward (mitigating the reflective warming effects).

Perhaps the reflective properties could be disadvantageous in hot environments whereby a reflective blanket could increase core body temperature (CBT) when used in a hot, humid environment. A 2015 study (5) suggests this is not the case. A randomized, controlled experimental design compared the effects of CBT cooling rates in

There is no current literature to support the use of reflective blankets as warming aids in a race setting. It seems as if speculation has guided decision making rather than letting science guide us.

four post exercise conditions: no blanket, blanket, recovery walking with blanket, and recovery walking with no blanket. The researchers attempted to bring the core temperatures of the participants up to a temperature that is commonly seen in endurance activity and then tracked cooling rates. They found 'no significant differences in CBT cooling rates that would have been caused specifically by the reflective blankets.' Further, there was no evidence that the use of reflective blankets prolonged the cooling periods of runners. (Which would be the case if radiant energy was a significant component of thermoregulation AND it was being effectively reflected.)

In summary, there is no current literature to support the use of reflective blankets as warming aids in a race setting. It seems as if speculation has guided decision making rather than letting science guide us. In fact, medical directors may want to consider the potential of detrimental effects to their racers. Could the distribution of reflective blankets give runners a false sense of security and, thus, delay their departure from race finishing shoots? Could this potentially lead to increased hypothermic effects due to prolonged evaporative and conductive cooling effects? I believe we should let science be our guide.

Dr. Greib holds academic positions at the Canadian Memorial Chiropractic College, National University of Natural Medicine, and the University of West Indies where he teaches methodology to improve athlete performance. He is the president of The SportLab, a specialized clinic located in Huntsville, Ontario, which offers consulting in sport injury rehabilitation to professional, Olympic, X-Games, and occupational athletes. He has also been the medical director for a variety of events including the Toronto Marathon, Limberlost Challenge Ultramarathon, and the IFSS Winter World Championships and is a marathon finisher himself (two-time Boston Marathon finisher with multiple qualifications and a PR of sub-3 hours). To contact Dr. Greib, write to start@thesportlab.ca.

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In Memoriam: Terry Kavanagh, MD

It is with great sadness that we announce the passing of Dr. Terry Kavanagh. He died at home at age 91 on September 10, 2018, from complications of metastatic skin cancer.

Dr. Kavanagh was not only one of the charter members of the American Medical Athletic Association (AMAA), he also frequently presented at AMAA's earlier symposiums at Boston, sharing his extensive knowledge as a pioneer in the field of cardiovascular health. During his 32-year tenure as medical director of the Toronto Rehabilitation Centre, one of the largest outpatient rehabilitation programs in North America, 25,000 patients passed through the program and benefited from his groundbreaking approaches. In fact, many AMAA members may recall when Terry brought seven recovering heart attack patients to run the Boston Marathon in 1973 and when, in 1985, he personally trained and ran the marathon with a heart transplant patient (the first ever to complete a marathon).

Dr. Kavanagh was also an active clinical researcher in his field. His early work concentrated on post-heart attack patients and establishing the benefits of exercise training, the effects of dehydration on distance runners, and the safety of marathon running. His later research contributed significantly to our understanding of exercise testing, prescription and training in heart transplant, and chronic heart-failure patients. His findings were published in more than 100 peer-reviewed journals and he authored three books: *Heart Attack, Counter Attack; The Healthy Heart Program;* and *Take Heart*.

In recognition of his endeavors, Dr. Kavanagh received countless prestigious honors and awards from organizations such as the American Heart Association, the American Association of Cardiovascular and Pulmonary Medicine, the Canadian Cardiovascular Society, and the American College of Sports Medicine. In 2003, he was honored by the University of Toronto, which conferred on him the degree of Doctor of Science, honoris causa, in recognition of his contributions. In 2006, he also received "The Living Legend" award from the World Society of Cardiothoracic Surgeons and, in 2013, on the occasion of the 150th Anniversary of Bayer Inc., he received an award as an outstanding Canadian, for his exceptional contributions to science and innovation in Canada.

Terry is survived by his loving wife, Johanna, who many AMAA members may also fondly remember. If you would like to honor his memory and support his work with cardiac patients, it is suggested you make a donation to the Cardiac Health Foundation of Canada for The Dr. Terry Kavanagh Heart Health Laboratory at the University of Toronto (www.cardiachealth.ca).

(Source: Toronto Star, September 15, 2018)

THANK YOU IIRM MEMBERS
for Your Support

The following individuals contributed to the IIRM Research & Education Fund at the Olympian, Patron, or Supporter level from January 1, 2018 to November 15, 2018. Donations help support our mission to educate and disseminate credible information as it pertains to all medical aspects of running and endurance events, as well as help promote research to facilitate improvements in clinical care at such events.

To make a contribution to the IIRM Research & Education Fund, go to www.racemedicine.org and click on the "Donations" icon on the home page. If you prefer to mail your contribution, please make your check payable to the International Institute for Race Medicine (or IIRM) and send to 12 Entrance Road, Plymouth, MA 02360. Be sure to include your name and contact information with the check so we can properly recognize you for your donation.

All donations are tax-deductible and individuals contributing at the Supporter level or above will receive a one-year IIRM membership (or renewal).

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We are Returning to Boston in 2019

The IIRM will be partnering with Northeastern University Bouvé College of Health Sciences and the Department of Physical Therapy, Movement and Rehabilitation Sciences to present the IIRM 2019 Sports Medicine Conference Series: Boston. This one-day meeting will be held on Saturday, April 13, from 8:00 am to 5:30 pm and will consist of morning lectures, an onsite lunch hosted by the IIRM, and afternoon workshops. Registration information will be posted by mid-December at www.racemedicine.org.

A room block for meeting participants and IIRM members has been reserved at The Colonnade Hotel, only a few blocks from Northeastern University. The rates for the three-night minimum stay are Friday: $309; Saturday: $379; Sunday: $379; and Monday: $309. To make a reservation, call 617-424-7000 and use the code "INT13A."

If you have questions regarding this event, please contact IIRM Meeting Coordinator Barbara Baldwin, MPH, at bbaldwin@racemedicine.org or call 240-271-1657.