WHATS NEW IN....

Rheumatology, Rehabilitation Medicine and Sports and Exercise Medicine

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Introduction

There have been many advances in Rheumatology, Rehabilitation Medicine and Sport and Exercise Medicine in both the clinical and administrative arenas. This article focuses on recent developments that show particular promise for treatment of military patients including Tumour necrosis factor (TNF) blockers in the treatment of ankylosing spondylitis and rheumatoid arthritis within rheumatology and the reorganisation of rehabilitation medicine services to allow a quick and more efficient return of personnel with multiple serious injuries, including amputees, to service.

Rheumatology

Rheumatology is a rapidly developing speciality as the underlying disease processes continue to be worked out providing novel therapies with a commensurate increase in costs. The Military Rheumatology Service is centred at the Defence Medical Rehabilitation Centre, Headley Court and this includes a rapid access synovitis clinic, an anti TNF facility and the recruitment of a clinical nurse specialist.

Seronegative Spondyloarthritis:

The spondyloarthritides (SpA) comprise 5 subtypes: ankylosing spondylitis (AS), reactive arthritis (ReA), psoriatic arthritis (PsA), enteropathic arthritis and undifferentiated SpA (uSpA). AS is the most frequent subtype (1) with an estimated prevalence of SpA of between 0.6 -1.9% and for AS between 0.1-1.1% (2-5). There are between 2100- 6650 SpA patients and 350-3850 AS patients serving in the Armed Forces. Traditional therapy is based on non steroidal anti-inflammatory drugs (NSAIDs) and physiotherapy, which is adequate in mild forms of the disease but therapeutic options for more severe disease have been limited until recently. The "biological agents", developed for the treatment of rheumatoid arthritis (RA), have also been used in the treatment of SpA. They target specific components of the immune system that play a role in the initiation and sustenance of the disease process. TNF mRNA has been detected in inflamed sacroiliac joints (6) and Sacroilitis and enthesitis are characteristic and almost pathognomic sites of involvement in SpA (7). Macrophages and activated T-cells secrete soluble TNF. It is key in the inflammatory response via its regulatory and effector actions on lymphocytic activation and release of cytokines (8). Two anti-TNF blockers are the only biologic agents licensed for the treatment of spondyloarthropathies (AS and PsA): Infliximab™, a chimeric monoclonal anti-TNF antibody and Etanercept™, a recombinant soluble p75 TNF-receptor-Fc fusion protein. Adalimumab™ a human monoclonal anti-TNF antibody may also soon get a licence.

Efficacy of anti-TNF agents in spondyloarthropathy:

Van der Heijde *et al* (9) have published the largest efficacy trial of Infliximab™ to date. Two hundred and seventy nine patients with active disease were compared to placebo were treated for 24 weeks. All outcome measures showed significant improvement with minimal drug toxicity. Improvements were seen within 2 weeks of starting the therapy and lasted for the trial duration. Open label extension studies (10-13) have shown sustained efficacy in AS patients for periods of 2-4years. In PsA a phase II trial (IMPACT) comparing Infliximab to placebo, the results showed significant improvement in arthritis, enthesitis, dactylitis and psoriasis (14). IMPACT II, the phase III, multinational, placebo controlled trial of Infliximab™ also confirmed significant improvements in arthritis and psoriasis (15).

Etanercept™ has a well established record in AS (16-18) and has been studied over a longer duration with sustained affect (11, 19). Interestingly the effect of Etanercept™ does not persist after cessation of treatment, but it's re-introduction shows equal efficacy and safety as in a treatment-naïve patient. Etanercept™ has an extensive phase II and phase III development programme in PsA, with striking results (20,21). The phase III study (14) showed significant improvements in the arthritis, psoriasis and quality of life. The results were sustained for 2 years in a follow on open label study (22). Etanercept™ has the ability to inhibit radiographic disease progression and significantly improve clinical symptoms.

Other treatments

Trials show promising results for the efficacy of Adalimumab™ in AS (23) and in PsA (24) and for bisphosphonates (25) and thalidomide (26) in AS. There is currently insufficient evidence to support the use of Anakinra™, an interleukin-1 receptor antagonist in AS.

Rheumatoid Arthritis

Rheumatoid arthritis is the most common chronic inflammatory arthritis (27). It has an estimated prevalence of approximately 1% in the UK general population (28) although this is less in the armed forces due to the younger mean age. The pathogenesis of RA remains incompletely understood but involves complex interactions between T and B lymphocytes, macrophages, fibroblast-like synoviocytes and involving a network of cytokines (29). Since the late 1990's new biologic treatments, in particular anti-TNF blockers have become well established in the treatment of active RA that responds poorly to traditional disease modifying anti-rheumatic drugs (DMARDs). For the past 2 decades RA has been considered a T cell mediated disease; more recently evidence has raised interest in a B-cell mediated theory of pathogenesis leading to B cell-directed therapy. There are many emerging therapies in RA including cell-targeted therapies; T cell depleting agents such as CAMPATH-1H and cytokine-targeted therapy such as inhibitors of interleukin-6. The most developed of the newer biologic therapies in RA is B cell depletion with rituximab, a CD20 monoclonal antibody.

B-cell depletion with rituximab

The CD20 antigen is present on the cell surface of all pre-plasma cell stages of B cell differentiation but the mature plasma cell loses the CD20 antigen. It serves as a good marker for B cells (30). Rituximab, a genetically engineered human-mouse chimeric monoclonal antibody against CD20 antigen has been used successfully in the treatment of B cell malignancies. An open-label study (31) demonstrated dramatic and sustained improvement in 5 patients with refractory RA. A further trial (32) of 161 methotrexate refractory RA patients compared 4 treatment groups, a control group of methotrexate alone, methotrexate plus rituximab, cyclophosphamide plus rituximab and rituximab alone. Rituximab alone or in combination provided significant and prolonged improvement in symptoms.

Rituximab is an exciting addition to the RA therapies and challenges the main theory of pathogenesis in RA for 20 years. Anti-TNF blockers have been successful in the treatment of DMARD refractory RA, but they are not a panacea. A substantial number of RA patients either do not respond or lose their initial response to treatment (33, 34). It is vital that there is continued development of new biologic agents such as rituximab.

Osteoarthritis

Osteoarthritis (OA) is the most common joint disorder (35) in the general population and is common in the armed forces. Chronic knee pain with radiographic features of tibiofemoral OA affects 10% of a population of 35-55yr olds (36). Non pharmacological treatments for OA include, exercise, education, weight loss, acupuncture, spa therapy and herbal remedies. Only education and exercise have significant evidence for their efficacy (37). Conventional oral and local pharmacological treatments such as paracetamol, NSAIDs and intra-articular corticosteroid all have grade 1A or 1B level of evidence for the treatment of OA (37). These treatments have no potential for a disease modifying effect unlike glucosamine and hyaluronic acid, the newest of the established OA treatments. Although both have been in use for over 20yrs it is only recently that use has become widespread. Glucosamine is a hexosamine sugar and is a basic building block in the biosynthesis of glycosaminoglycans, which with collagen forms articular cartilage (38). In the last 20 years the scientific evidence to support its use has been increasing (39-44) and a number of systematic reviews and meta-analyses have concluded that glucosamine is efficacious in the treatment of knee OA (37,45-47). However, since 1999 there have been a number of contradictory trials concluding that glucosamine had no benefit over placebo in knee OA (48-52). Towheed *et al* (53) from the Cochrane Collaboration revised their 2004 review after looking more critically at the methodology and funding of previous positive studies and concluded that glucosamine showed no superiority over placebo for pain or function. It is difficult to compare these clinical trials in a systematic review due to heterogenicity of trial design, differences in glucosamine products and doses and differences in populations. The National Institution of Arthritis and Musculoskeletal and Skin Disease in the USA have funded a multicentre controlled study involving 1600 patients over 6 months comparing different compounds of glucosamine with a COX-2 inhibitor and placebo. Hopefully this trial will give a more definitive answer about the efficacy of glucosamine.

Hyaluronic acid (HA), a high molecular weight polysaccharide, is a major component of synovial fluid and cartilage. In osteoarthritis, the molecular weight and concentration of HA is diminished. The concept of viscosupplementation suggests that intra-articular injection of HA could help restore the viscoelasticity of the synovial fluid. HA has a multiplicity of biological actions (54). HA has evidence for a disease modifying effect and for improvement in symptoms and function (55). HA can provide pain relief lasting for several months (56), although there may be a slow onset of action and the need for up to 3 intra-articular injections per treatment.

Cyclo-oxygenase-2 (COX-2) inhibitors also have grade 1A level of evidence for their

efficacy in knee osteoarthritis (37). COX-2 inhibitors are under scrutiny after rofecoxib™ was withdrawn due to associated increased risks of cardiovascular complications. A recent study by Johnsen *et al* (57) demonstrated increased risk of hospitalisation for MI in users of rofecoxib™, celecoxib™, other COX-2 inhibitors and other conventional non-aspirin NSAIDS. The highest relative risks were found among new users of these drugs. With significant cardiovascular side effects in COX-2 inhibitors and traditional NSAIDs newer disease modifying drugs with good safety records, such as glucosamine and hyaluronic acid, potentially have a huge role in the future management of OA.

Osteoporosis

Osteoporosis is common in the general population particularly in elderly females - 70% are osteoporotic by the age of 80yrs(58). In the Services the prevalence of post menopausal osteoporosis is predictably much lower, but in the small but significant number of spinal cord injuries in the armed forces osteoporosis of the hip and knee becomes a significant problem (59).

Lifestyle changes are the initial treatment in osteoporosis, including weight-bearing exercise, increased dietary intake of calcium, adequate sun exposure for Vitamin D activation, cessation of smoking and reduction of alcohol intake. Treatment with calcium and vitamin supplementation, and in particular bisphosphonates, revolutionised the therapeutic approach to osteoporosis. Bisphosphonates do have significant side effects, notably gastro-oesophageal reflux and may sometimes fail clinically due to anti resorptive rather than anabolic action. Teriparatide™, a parathyroid hormone analogue, has recently been licensed for the treatment of osteoporosis. Studies show that teriparatide increases bone mineral density and decreases the risk of vertebral and non-vertebral fractures in patients with previous vertebral fractures (60, 61). It is useful in the treatment of bisphosphonate refractory osteoporosis.

In female soldiers we should be aware of the athletic triad of poor diet, low weight and amenorrhea. This is certainly a cause of low bone mineral density and resultant stress fractures(62).

Summary

Spondyloarthropathies and rheumatoid arthritis have increased therapeutic options from a decade ago. Traditional therapy of exercise and NSAIDs remain the mainstay of treatment for the spondyloarthropathies, but for patients with active disease anti-TNF antagonists should be considered. The therapeutic armoury is increasing for RA as our knowledge of the pathophysiology improves. Osteoarthritis is the most common cause of joint disease but the control of symptoms improves as the understanding advances. Osteoporosis, although not common within the military, should be considered in the context of the athletic triad and again there have been major advances in therapy.

Rehabilitation Medicine

The recent developments in military medical rehabilitation are the most significant ever. They link the Defence Medical Rehabilitation Centre (DMRC) with the operational role, specific clinical delivery for the more seriously injured musculoskeletal and neurological patients and provide provision in primary care for assessment and rehabilitation. They include the development of the Defence Medical Rehabilitation Evaluation & Co-ordination Cell (DMRECC), the implementation of the Defence Medical Rehabilitation Plan (DMRP) and the Deployed Medical Rehabilitation Team (DMRT) and the specific provision for amputees and those with complex injuries. These developments in Service rehabilitation are based upon the principles of the system of 'End to End Care' from operational theatre to return to duty as broadly described in The Defence Health Plan (63).

The Defence Medical Rehabilitation Plan/Programme (DMRP)

The DMRP is directed by Director Healthcare and is now the Defence Medical Rehabilitation Programme. The DMRP provides Primary Care Rehabilitation Facilities (PCRF) and Regional Rehabilitation Units (RRU) as a means of delivering tiered medical rehabilitation across the Services. They offer local rapid intervention during the acute phase of a musculoskeletal injury and triage of patients who require specialist rehabilitation services or other secondary care input. They offer a multidisciplinary approach of a primary healthcare medical opinion, physiotherapist and Remedial Instructor (RI). This ensures early assessment and treatment of musculoskeletal injuries with the aim of early return to duty.

RRUs are larger, regional establishments designed to cater for more complex patients requiring more intensive rehabilitation, which a PCRF may not be able to provide. These offer access to specialist advice and assessment, offering periods of intensive rehabilitation for more serious and complex injuries. They are also intimately involved in the 'fast-track' system to orthopaedic surgeons. There are currently 14 RRUs established in the UK and BFG.

DMRC sits at the 'hub' of these facilities, acting as the 'alma mater' of DMS rehabilitation service. It manages patients with the most complex injuries. The system is fluid, allowing patients to move as necessary through the various rehabilitation providers,

ensuring they get access to the full scope of services as needed. With these facilities it will be possible for rapid access to effective rehabilitation services close to the individual's home unit area.

Operational Medical Rehabilitation

The incidence of musculoskeletal injury during all phases of military operations is substantial (64-67). The provision for assessment, treatment and rehabilitation particularly in theatre has previously been *ad hoc*. The need is for early assessment, diagnosis, compilation of an effective clinical plan and provision for co-ordinated rehabilitation either in theatre or on return to the UK or BFG.

According to the Aeromedical Evacuation Co-ordination Cell (AECC) there are approximately 70-80 evacuations per month of soldiers serving overseas of which approximately 70% are musculoskeletal in nature. This reflects similar statistics from other conflicts (64,65,68,69). Whilst some require immediate hospitalisation in UK, a significant number could be managed in theatre or via early appropriate referral to the DMRC or a Regional Rehabilitation Unit (RRU) on return to UK or BFG. The care pathways are illustrated in Figure 1.

Crisis resolution and post conflict operations will often be protracted. Maintaining sufficient numbers of operationally fit personnel is critical. It is essential, that injured personnel receive rapid, effective access to treatment and rehabilitation to ensure return to duty as soon as possible. Furthermore, there have been several high profile cases in the media of injured service men and women reportedly having received poor medical management following evacuation from operational theatres. These have varied in nature from patients being 'lost' within the NHS system, or, more emotively, a perceived lack of effective care. This may be damaging to the morale of Service personnel and the reputation of the Services.

The development and introduction of the DMRT combined with the amendments to the aeromedical evacuation procedure, the restructuring at DMRC and the establishment of RRU has combined to ensure that rehabilitation can be delivered from operations to UK / BFG. The arrangements for patients who suffer musculoskeletal and neurological injuries on operational deployments are in Surgeon General's Policy Letter 22/5 (70)

Deployed Medical Rehabilitation Team (DMRT)

The role of the DMRT is to act as a 'Force Preserver', by assessing, treating and returning musculoskeletal injured personnel to operational levels of fitness as quickly as possible. The DMRT has been developed to provide operationally appropriate assessment and treatment of personnel with musculoskeletal injury within theatre. This ensures that injured individuals can effectively and rapidly be returned to deployable operational levels of fitness where possible. The Team is small with a high degree of clinical expertise to address a substantial operational clinical need. A DMRT comprises a Consultant in Rheumatology and Rehabilitation (R&R) providing clinical opinion, a Physiotherapy Technical Officer (Clinical Specialist) and a Remedial Instructor (RI). It can deploy attached to a Role 2 or 3 medical facility.

The DMRT ensures that injured personnel can receive effective assessment and treatment as far forward as possible. The aim is to determine whether a patient can be retained in theatre or evacuated. In the latter case, the DMRT will ensure effective co-ordination of care for evacuated patients.

When there is a need for medical evacuation the DMRT liaise with the aeromedical evacuation liaison officer (AELO) and ensure that there is an appropriate rehabilitation plan in place on return to the UK or BFG.

The Defence Medical Rehabilitation Evaluation Co-ordination Cell (DMRECC)

DMRECC is based at DMRC. Its role is to provide the co-ordination of case management for patients with musculoskeletal conditions and those with more complex rehabilitation needs. DMRECC has two main roles:

- Administrative: The Medical Administrative team has established links with RCDM MPAC/AELO and Aeromedical Evacuation Control Cell (AECC). They ensure that the administrative co-ordination of care pathway for patients from the point of entry into UK until returned to full fitness or medically discharged from the Service. BFGHS will be responsible for co-ordinating the management of patients returned directly to BFG.
- Clinical: Consultant led Multi-disciplinary team provide the clinical assessment and decisions on the most appropriate care pathway for each patient.

DMRC Developments

DMRC offers access to all aspects of multidisciplinary rehabilitation with on-site Consultants, physiotherapists, remedial instructors, occupational therapists, speech and language therapists, social workers and psychology. It has 5 gymnasiums and a large hydrotherapy pool to support the clinical departments. The medical records department, workshops for the production of prosthesis, logistical and administration staff support DMRC's clinical role. DMRC is in

a period of rapid change and development. This is a direct consequence of the requirement for a better co-ordinated provision for injured personnel returning from operations, overseas or in the UK. DMRC has recently become the Services' rehabilitation provider for patients requiring complex rehabilitation, amputee management and prosthetic limb fitting, and the co-ordination of patients with musculoskeletal injuries returning from operational theatres. These developments have occurred within DMRC. Specifically these developments include:

- The establishment of the DMRECC
- Expanded Ward; Previously 36 beds were established at DMRC with staffing for 18 neurological rehabilitation beds. This is now expanded to include provision for polytrauma and amputees who previously would be rehabilitated at a Regional level with varying provision.
- Amputees Provision; DMRC is the Defence Medical Services amputee centre. When amputees are sufficiently stable and have reached the required level of recovery, they will be transferred directly to DMRC for rehabilitation. This service will include limb fitting and prosthetic provision. They will be accommodated in the newly staffed ward bed spaces. Funding for this has been secured from DHealthcare and Chief Executive DMETA. This will allow service personnel to be fitted with appropriate limb for their current level of function and employment in a Service Environment with Service ethos.

Summary

The benefits from these arrangements include:

Optimal, co-ordinated clinical assessment and care at the appropriate time and place. There should be no scope for patients becoming 'lost' in the system due to poor tracking.

The system is intended to ensure injured personnel are provided with a comprehensive, co-ordinated and optimally effective care package. This 'end to end' vision should mean that the DMS does not lose or mismanage individuals who are deserving of the best care that is available, allowing them a rapid return to fitness.

Commanders will obtain an early indication of availability for return to duty, with the care plan be optimised for this purpose.

Needless admission to RCDM will be considerably reduced and hopefully eliminated, thereby reducing expenditure.

The process meets the requirements of a managed health system, improving clinical effectiveness and financial efficiency.

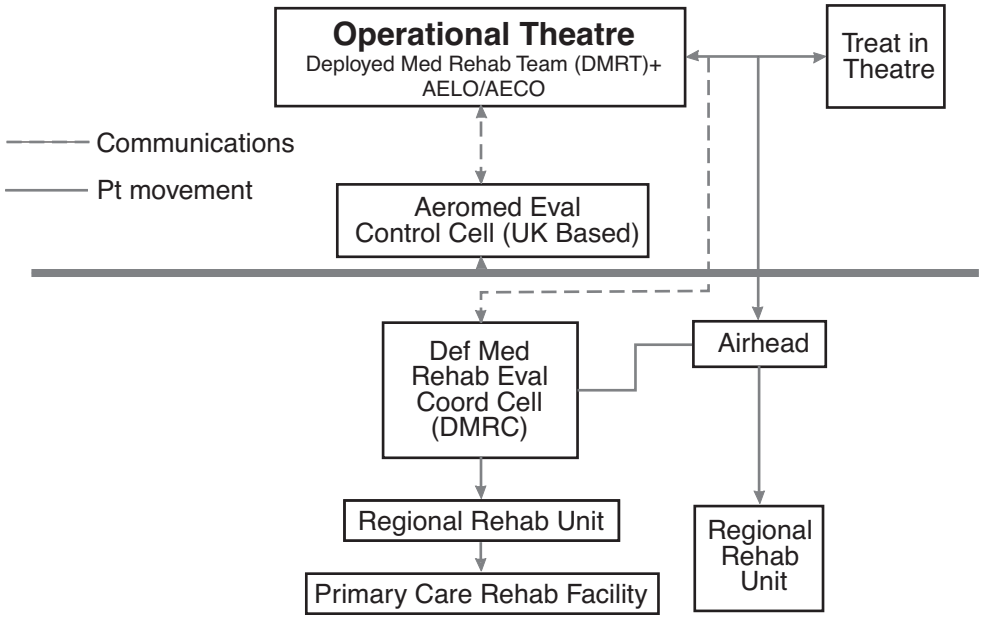

Figure 1a : Arrangements for operational patients with musculoskeletal injuries NOT requiring hospitalisation

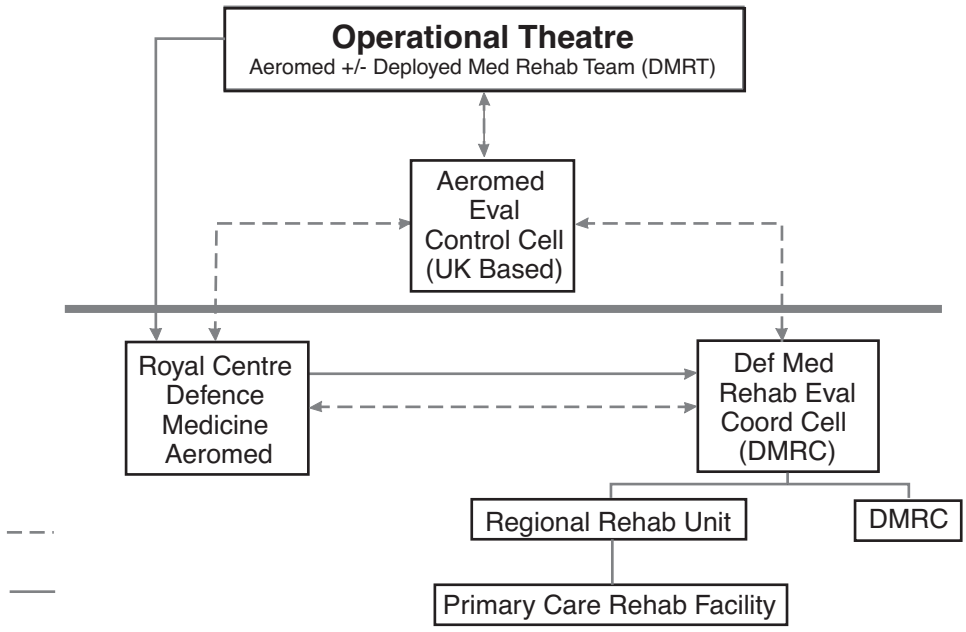

Figure 1b: Rehabilitation Arrangements for Patients requiring transfer to RCDM

Sports and Exercise Medicine

From the 30th September 2005 Sports and Exercise Medicine (SEM) has been recognised as an independent speciality within the UK and can be entered on the General Medical Council's Specialist Register. The speciality has been allocated 9 National Training Numbers and training will be organised by the new Faculty of Sport and Exercise Medicine (UK). These are exciting times for doctors involved in the field and the London 2012 Olympics should result in increased sport participation and facilities, increasing the demand for specialists in SEM, and boosting this fledgling speciality.

The benefits of exercise have been demonstrated in a variety of fields, from improving symptoms of depression in stroke survivors (71), to improved motor function in Parkinson's sufferers (72). Studies in the elderly have also shown the benefit of exercise in fall reduction. In addition, exercise can be used to reduce the risk of injury in sports when applied correctly, as evidenced by a study (73) showing a structured warm-up programme significantly reduced lower limb injuries in young sportsmen. It is important that exercise is prescribed correctly, with attention given to type, frequency and intensity, as well as being subject to review. SEM specialists have an opportunity to fulfil this role and ensure patients receive the correct 'dose'. A recent study (74) showed that in a survey of 50,000 adult arthritis sufferers, less than 50% had ever been advised to be more physically active,

despite extensive data showing its benefit in this patient group. Improved epidemiological studies are increasing our knowledge of sport and exercise injury incidence rates, and are being utilised to identify areas of need. Research in the fields of pathophysiology and genetics is increasing our knowledge of the body's response to exercise and injury, and offering the opportunity to develop novel treatments and rehabilitation techniques. Some also offer the potential for abuse, and regulating their use may prove difficult.

Genetic Research and SEM

There has been considerable interest in genetic testing to aid in the selection of future champions. Studies over the last 20 years suggest genetic factors explain between 25 - 70% of inter-individual differences in maximal and sub-maximal oxygen consumption and skeletal muscle metabolism. If the genes associated with athletic performance can be determined, individuals who have the genetic potential to be successful can be identified early. Two particular genes have shown potential in this area.

The ACTN3 gene produces a protein called alpha-actinen-3, which is found in skeletal muscle and involved in the process of muscle contraction. It is predominately found in 'fast twitch' muscle, and contributes to the ability of these muscles to generate forceful muscle contraction at a high rate of repetition. Everyone has two copies of the gene. One variant, known as the R577X variant, stops the muscle cell reading the entire ACTN3 gene. If an individual has two copies of the R577X variant, they are unable to produce alpha-actinen-3 protein, and it is absent from the muscles. The gene ACTN2 compensates for this loss, though the protein it codes for is less effective. In Europeans, studies have shown that 18% of the population has this genotype. Research at the Australian Institute of Sport (75) showed a statistically significant lower frequency of the R577XX genotype in power athletes versus controls. In addition endurance athletes showed a higher frequency for the R577XX genotype, though this was only statistically significant in females. It was also noted that all Olympic standard power athletes had at least one copy of the ACTN3 gene without the R577X variant. Commercial laboratories now offer ACTN3 gene testing to athletes, with the aim of tailoring their sporting participation and training to their genetic make-up.

The Angiotensin-Converting Enzyme (ACE) gene has an insertion (I) variant and a deletion (D) variant. The I variant appears to confer endurance performance (76), the D variant appears to be associated with muscle growth and confers an advantage in power sports (77). A Spanish study (78) looked at the frequency of these variants in three groups, professional cyclists, sedentary controls, and elite runners. The proportion of genotype expression was statistically significant between the three groups. The DD genotype was highest in cyclists (50%), ID highest in sedentary controls (46.2%), and the II highest in runners (40.7%). A study in professional footballers and the ACE genotype showed no dominant genotype pattern. Other genes that have been linked to performance include the muscle specific creatine kinase (CKMM) gene and genes of mitochondrial DNA. These studies have been less conclusive.

The concern with gene identification is the potential for this research to lead to reduced sport participation, with a lack of 'star' genes possibly leading some to give up sports. At the moment it is important we encourage sport participation as much as possible. In addition, concentrating on genotype doesn't allow for the significant impact of environmental and psychological components in the make up of any champion athlete.

Recently there has been increasing alarm at the threat of gene doping in the pursuit of sporting excellence. Current anti-doping practices rely on the presence of detectable substances to identify those abusing performance enhancing products. Manipulation at a cellular level may well prove undetectable and gene therapy offers an opportunity to do this. Research into muscle wasting conditions and forms of anaemia may provide potential avenues of abuse. This potential abuse method, along with the inherent problems associated with anti-doping practices, has led some physicians (79) to call for an end to drug testing in sport, and a switch to assessments of fitness to compete instead.

Advances in soft tissue repair

Soft tissue injuries are the commonest sporting injury. A study (80) of English professional rugby union players showed that at any one time a team will have 23% of players unavailable for selection, the majority due to muscle injuries. They have been traditionally treated using the acronym RICE (Rest Ice Compression Elevation). NSAIDs have been used to reduce swelling and pain levels, but their use is controversial. There is concern that their use may impair tissue repair. Shen *et al* (81) demonstrated that a Cox-2 inhibitor resulted in impaired healing and more fibrosis than in controls. Prisk *et al* (82) showed that NSAIDs were useful initially, but resulted in impaired tissue function and histology. A study on pre-event NSAIDs has shown a significantly negative effect on renal function, potentially precipitating hyponatraemia and cerebral oedema (83).

Research into inflammation, and the cytokines and cells involved, is giving us a greater understanding of the injury process. This opens up the possibility of influencing tissue repair at a molecular level, improving recovery and reducing fibrosis. Muscle injury results in a repair cascade (84). Muscle fibres degenerate during the first few days, exacerbated by inflammation and other immune responses. Regeneration starts at one week, peaks at two weeks and diminishes at a month. This process is controlled by growth factors, which influence satellite (stem) cells and myoblasts, promoting differentiation into myofibres.

This results in muscle repair. The formation of scar tissue (fibrosis) begins two to three weeks post injury and limits the regeneration of muscle. The two main approaches to aiding muscle repair are either augmentation of the regeneration phase or limitation of the fibrosis phase. Research has shown growth factors to be powerful agents of myofibre differentiation and growth. Growth hormone induces the production of these factors and results in muscle hypertrophy. Research is identifying the individual factors involved and the possibility of more targeted therapies. Mechano Growth Factor (MGF) is an Insulin-like Growth Factor (IGF-1) derivative produced locally in muscle tissue. It is produced in response to mechanical stimulation and, along with muscle IGF-1, provides a direct link between physical activity and gene expression (85). MGF is thought to have a significant tissue repair role, activating satellite (stem) cells released by muscle damage, which donate their nuclei to damaged muscle fibres to enhance regeneration (86). Further research is identifying more IGF-1 subtypes, with the aim of defining the specific roles of each in the process of muscle adaptation, hypertrophy and repair. The potential application of targeted IGF subtypes may provide a method of enhancing muscle repair. Studies have already shown success in using viral vectors to deliver genes to injured skeletal muscle, and induce regeneration (84). The downside of the use of these agents is the fact that they do not appear to reduce fibrosis, thus limiting the ability of the muscle tissue to regenerate completely.

Commercial production of specific IGF subtypes opens the opportunity for abuse, particularly in power sports. Agents aimed at reducing fibrosis post injury are therefore ethically more attractive.

Transforming Growth Factor-1 (TGF-1) has been implicated in the development of fibrosis in various tissues. In Duchennes muscular dystrophy (87) and dermatomyositis (88) it is expressed in high levels in muscle biopsies and is associated with fibrosis formation. High levels are also seen in skeletal muscle damage animal models (84). TGF-1 is therefore thought to have an important role in the fibrotic cascade and blocking it could potentially limit fibrosis. Relaxin, an insulin-like growth factor, has been shown in animal studies to decrease myofibroblast proliferation and down-regulate expression of fibrotic proteins in vitro, enhancing muscle regeneration, reducing fibrosis, and improving injured muscle strength *in vivo* (89). Suramin, a heparin analogue, blocks the stimulatory effect of TGF-1 on muscle-derived fibroblasts in vitro. In mice it reduces fibrous scar formation and enhances strength in injured skeletal muscle (90). The next step for these agents will be human trials. Stem cell research is showing potential benefit in the repair of soft tissue injuries. Mesenchymal stem cells have been harvested from the sternums of injured race horses (91), and injected into damaged tendons with good results. The treated horses appear to show increased rates of healing with no significant complications from the procedure, though the research is far from conclusive. The potential to extend this therapy to humans shows great promise.

The role of eccentric exercise therapy

Overuse tendon injuries represent a significant percentage of a sports medicine clinic caseload. Biopsies of these tendons shows no inflammatory cell infiltrate, and biochemical mediators of inflammation are found in levels similar to controls (92) but the tendon extracellular matrix is substantially altered (92). Hence they are referred to as cases of tendinosis or tendinopathy.

Eccentric contractions are those that occur as the muscle fibres are lengthening, as in the lowering phase of a bicep curl. Eccentric training has been found to be beneficial in the treatment of chronic tendon problems (93). Stanish *et al* (94) and Renstrom *et al* (95) proposed that tendon overuse injures were a result of the macro- and microscopic disruption of the tendon under specific conditions of eccentric loading. They suggested that any successful rehabilitation programme should incorporate these exercises in the treatment.

Eccentric exercises have been shown to be of benefit in the treatment of Achilles (Figure 2) and patellar tendinopathies. In addition they have also shown good results in the treatment of lateral epicondylitis (tennis elbow) (96), and have been used successfully to treat patello-femoral pain syndrome in military patients (97). They form an important part of the rehabilitation programme for this condition at DMRC, Headley Court.

Most Achilles tendinopathy studies have looked at 12 week programmes and shown a significant benefit from this sort of exercise, in terms of activity, reduction in pain, and function (98-100). Improvements have also

been seen on ultrasound (100) and MRI (101), with decreased tendon volume and improved intratendinous signal. When the tendon pathology is insertional, rather than mid-tendon, the effectiveness of therapy drops from 90% to 33% (102). The benefit from eccentric exercise therapy has also been successfully shown in the treatment of patellar tendinopathy (103). Studies (104,105) have proposed that these exercises should be carried out on a decline board. This increases the load on the knee extensor mechanism by reducing the passive and active influence of calf tension as the ankle is dorsiflexed. There is often the presence of neovascularisation in the area of degeneration. New vessel growth has been shown to be associated with the pain felt from such injuries (106), possibly due to the sensitivity of accompanying small nerves. These vessels are identifiable using power doppler ultrasound. Injecting sclerosants into these areas has been shown to be of benefit in reducing pain levels (107), and can be used in conjunction with an eccentric programme to improve the time taken to return to activity.

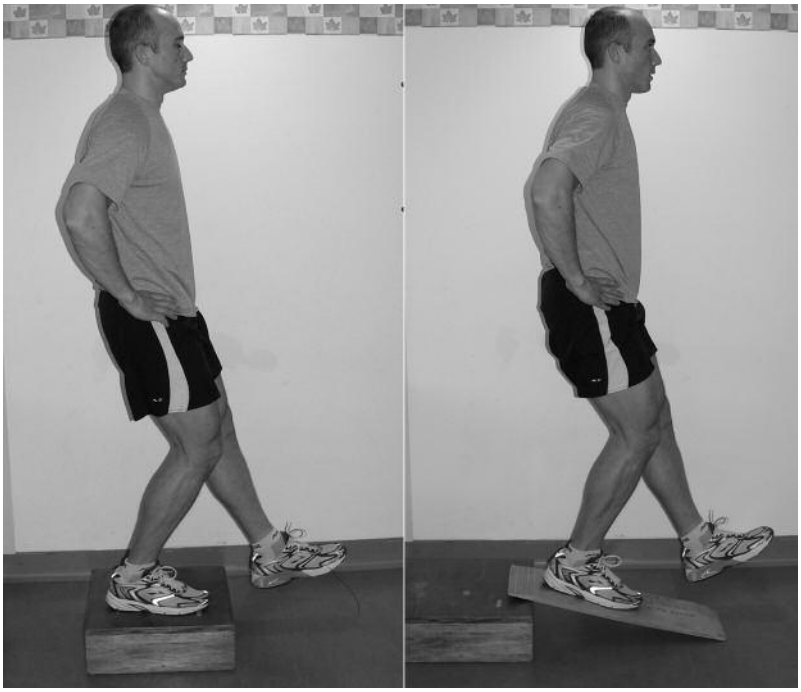

Figure 2: Inclined eccentric loading programme

However, a note of caution needs to be sounded. When eccentric exercises were added to the daily routine of volleyball players during a season (108) they were ineffective at reducing levels of discomfort. Eccentric exercises place significant demands on exercising muscle and their use must include a reduction in other training activities. Current protocols for eccentric exercises are varied, and more research is needed in this area to elucidate the most effective programme.

Conclusion

The field of SEM is greatly benefiting from research into the genetics and cellular processes of tissue repair, and these have the potential to lead to the development of exciting new treatments. Quality epidemiological studies have started to identify areas of need and influenced current thinking. However it is also important that the speciality realises that further research into current therapies is needed if a solid evidence-based practice is to be developed.

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