Title

Osteoarthritis in the United Kingdom Armed Forces: A Review of Its Impact, Treatment, and Future Research

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Word count: 2996

Ethical Approval: This study did not require ethical approval – it does not involve human or animal participant data.

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Abstract

Within the UK Armed Forces, musculoskeletal injuries account for over half of all medical downgrades and discharges. Data from other Armed Forces show that osteoarthritis (OA), more common in military personnel, is likely to contribute to this, both in its primary form and following injury (post-traumatic OA, PTOA, which typically presents in the in third or fourth decade). OA is not a progressive 'wear and tear' disease, as previously thought, but a heterogenous condition with multiple aetiologies and modulators, including joint damage, abnormal morphology, altered biomechanics, genetics, low-grade inflammation, and dysregulated metabolism. Currently, clinical diagnosis, based on symptomatic or radiological criteria, is followed by supportive measures, including education, exercise, analgesia, potentially followed by surgical intervention, with a particular focus on exercise rehabilitation within the UK Military. Developments in OA have led to a new paradigm of organ failure, with an emphasis on early diagnosis and risk-stratification, prevention strategies (primary, secondary, and tertiary), and improved aetiological classification using genotypes and phenotypes to guide management, with the introduction of biological markers (biomarkers) potentially having a role in all these areas. In the UK Armed Forces, there are multiple research studies focussed on OA risk factors, epidemiology, biomarkers, and effectiveness of different interventions. This review aims to highlight OA, especially PTOA, as an important diagnosis to consider in serving personnel, and outline current and future management options and detail current research trends within the Defence Medical Services.

Word count: 234

Key Messages

What is already known on this topic;

- Musculoskeletal injuries are the leading cause of medical downgrade and medical discharges within the UK Armed Forces, with osteoarthritis (OA) contributing significantly to this burden.
- OA is a heterogenous synovial joint disease, with multiple aetiologies and contributing factors, leading to a clinical syndrome of pain, stiffness, increased physical inactivity and reduced function; more common in military personnel, in both the primary, idiopathic form, and the secondary, post-traumatic form (PTOA).

What this study adds;

- Currently under-recognised within the UK Military, this review of OA aims to articulate the importance, and impact, of this common and disabling condition by discussing underlying pathophysiological mechanisms, the contribution of individual and risk factors and current management options.
- This study introduces new concepts into the military, such as a model of 'organ failure' for OA, the role of differing prevention strategies to mitigate or slow disease progression, and use of phenotyping and biomarkers to guide risk-stratification and interventions.

How this study might affect military practice or policy;

- This study aims to highlight OA and PTOA as diagnoses to consider especially in those with prolonged joint pain following traumatic injury by demonstrating evidence-based current and future clinical management to guide best practice of those at risk or diagnosed with OA and highlighting the future research trends within the Defence Medical Services and how these will offer the potential to improve the management of OA for service personnel.

Background

Musculoskeletal injuries (MSKI) are a significant burden for the UK Armed Forces, accounting for 54% of medical discharges between 2015 and 2020 and 56% of medical downgrades between 2010 and 2020.[1] As a result, the Defence Medical Services (DMS) prioritises MSKI research to understand the epidemiology, causes and mechanisms in order to optimise existing and develop new prevention, mitigation, and management strategies.[2] Typically, these injuries occur during the initial stages of training, after strenuous activity, or as a result of trauma, most commonly affecting the lower limbs and spine.

A key and under-acknowledged pathology in the UK military population is osteoarthritis (OA), accounting for 10% of all US military MSKI-related discharges.[3-4] OA is a synovial joint organ disease characterised by progressive deterioration and loss of articular cartilage, resulting in structural and functional changes in the joint's synovium, meniscus, ligaments, and bone.[5] The National Institute of Health and Care Excellence (NICE) recommends pragmatic clinical diagnosis of OA in those ≥45years old, following three months of joint pain, made worse by activity.[6] This condition affects approximately 6.5 million people in the United Kingdom and is one of the leading causes of disability on a global scale due to increased physical inactivity and associated development of cardiometabolic disease and other co-morbidities.[6-7]

Previously thought to be a progressive "wear and tear" degenerative disease, it is now understood to be a heterogenous process with distinct underlying pathophysiological pathways, and the interaction between modifiable and non-modifiable risk factors and individual features (Figure 1). Significantly, OA is more prevalent among military personnel due to their physically demanding jobs and increased risk of specific exposure to trauma and vibration.[8-9] In addition, a distinct subtype, post-traumatic osteoarthritis (PTOA), is common in military populations due to increased exposure to major or repeated micro trauma.[4,10] Due to its accelerated pathophysiological process and typical manifestation in the third or fourth decade, PTOA can have a long-lasting impact on individuals and their occupations.[11] A recent study showed that, following a knee injury, 1 in 6 US Military Officers developed OA by age 30.[10]
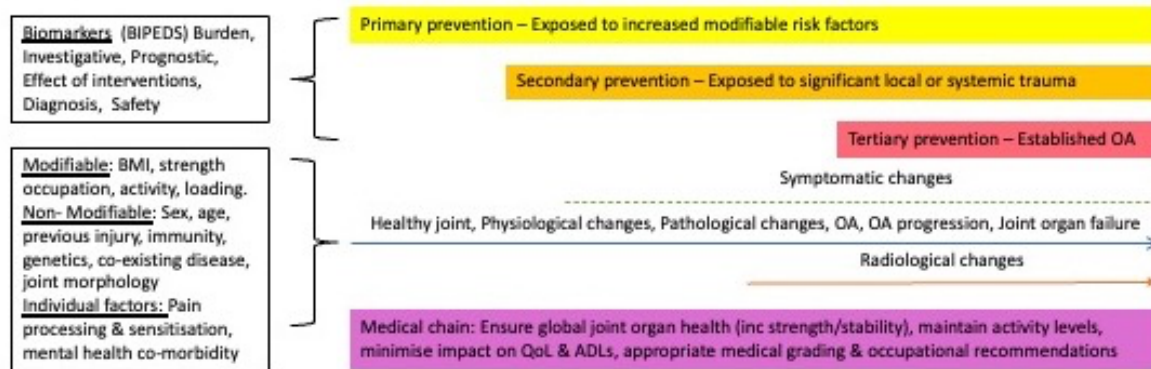
Figure 1. Overview of individual and risk factors contributing to the spectrum of Osteoarthritis and potential role of biological markers throughout the disease continuum, in support of primary, secondary and tertiary prevention strategies of the medical chain.

OA: Osteoarthritis, ADL: Activities of Daily Living, QoL: Quality of Life, BMI: Body Mass Index

The purpose of this paper is to highlight OA, specifically PTOA, as an important diagnosis to consider in the military population to improve awareness and appropriate diagnosis, suggest current and future management options, and introduce current research trends.

Post-traumatic Osteoarthritis

PTOA develops following traumatic injury, with certain injuries, such as cruciate ligament rupture, meniscal tear, and patella, ankle or shoulder instability strongly linked to subsequent development.[12] It has been estimated that 13% of knee PTOA can be attributed to previous trauma.[12] The initial traumatic episode results in localised disruption of articular cartilage, cartilage fissures, and chondrocyte death, accompanied by a posttraumatic inflammatory response and synovitis, as well as concurrent damage affecting biomechanical function of the joint, including fractures.[4,13-14] It is not solely irreversible mechanical damage that leads to PTOA, but a combination of enduring chronic inflammation, hypoxia, biomechanical changes, genetic factors, and individual predispositions, with symptoms appearing within two-five years of initial injury.[9,12,15]

Pathophysiological mechanisms

After an injury, the joint undergoes activation of multiple signalling pathways, resulting in cartilage matrix degradation and synovial inflammation leading to a process of repair, remodelling, and adaptation.[14] However, aberrant mechanistic pathways can contribute to a lack of repair and

remodelling, inadequate adaptation, and the subsequent development of OA, with altered joint biomechanics, metabolism, and low-grade inflammation all playing crucial roles.[7,12] OA is a heterogenous condition, and the balance of each contributing factor is likely to be different. Differences can be described as the endotype, related to the contributing mechanism, or the phenotype, relating to the condition's presentation (see Table 1). Studying differing phenotypes allows understanding of their underlying inflammatory pathway, metabolic and biomechanical changes, setting the conditions for optimised and personalised interventions.

Genotype	The complete genetic material of an individual, inclusive of specific variants
Phenotype	Observable characteristics - interaction between genotype and environment. Can include physical characteristics such as symptoms, biochemical, and physiological characteristics
Endotype	Condition subtype distinguished by distinct causes or mechanisms, allowing identification of subgroups who require different treatments
Endophenotype / Intermediate phenotype	Measurable characteristics related to a particular disease, influenced by genetic factors. They are more proximal to the underlying genetics of the disease than visible clinical symptoms, therefore closely tied to the underlying biological mechanisms. Studying intermediate phenotypes and underlying genetic risk factors and biological mechanisms, allow identification of disease endotypes and effective targeted treatments

Table 1. Classification of typing and applicability to osteoarthritis management

Inflammation, both local and systemic, plays a key role in the initial pathogenesis and ongoing progression, often demonstrated by the presence of joint synovitis and effusion.[16,17] In contrast to inflammatory arthritides, such as rheumatoid arthritis, the inflammation is 'low-grade', with standard histological staining revealing low-moderate inflammation in OA synovial tissue.[17] This ongoing inflammatory response offers an insight into OA development and progression, and a potential target for pharmacological intervention.

Joint surface incongruity and instability (against which, periosteal cells and the synovium form osteophytes) also contributes, leading into joint biomechanical changes, influencing weight bearing, gait and overall joint function.[14] This is reinforced by activation of mechano-signalling pathway, and resultant mechanoinflammation.[13] Biomechanical-based physical rehabilitation interventions can improve function and negative feedback loop of ongoing inflammation, and research into limited surgical techniques, such as joint distraction, shows restoration of the mechanical and biochemical joint environment.[13,18]

Changes in the synovial fluid composition, due to synovial injury, hypoxia and haemarthrosis, are also involved. Recent research has demonstrated that these alterations can, for instance, result in insufficient lubrication of the joint boundary, thereby diminishing joint function.[19] In addition, changes in synovial fluid provide an immediate window into the local environment, and the current practise of compensated polarised light microscopy to identify crystal arthropathies such as gout (negatively birefringent) or pseudogout (positively birefringent) could be extended to investigate the predominant OA pathological process.

Further mechanisms relate to metabolic processes, including the interactions between glucose and lipid pathways.[20] Metabolic syndrome is felt to potentially have a bidirectional relationship with prolonged inflammation and activation of the innate immune system, further contributing to the ongoing dysregulation and pathological processes, causing accelerated OA progression and increased pain modulation.[7,21] Animal studies suggest hypercholesteremia, dysregulated lipid metabolism and cholesterol accumulation are associated with the development and progression of OA, meaning that dietary interventions, weight optimisation and medication might help to reduce and reverse this process.[21]

Risk and individual factors

Modifiable and non-modifiable risk factors increase the likelihood of OA development and progression (Figure 1). Females are both more likely to develop OA and suffer sporting injuries.[7] Preceding joint injury, both traditional MSKI and combat-associated injuries such as amputations contributes through altered loading,[22] and by increasing physical inactivity, body mass index (BMI) and impairing physical function.[11,15] High BMI increases OA risk by up to 30%, often preceding the onset, exhibiting bidirectional causality with both conditions influencing each other. Concurrent joint disease, as well as joint alignment, morphology and muscle strength can lead to poor biomechanics and mechanoinflammation.[13] Non-modifiable risk factors include sex, genetics, and immunological predisposition. Individual factors, such as pain processing, sensitisation and modulation, and anxiety, depression, and other mental health conditions, can affect the individual's experience of OA.[7]

Management options

Joints, particularly large joints, should be treated as organs: complex structures containing a variety of tissues with a common aim, to allow load transfer and movement. Joint injuries are organ injuries causing intermittent, or prolonged, dysfunction potentially leading to joint organ

failure requiring external clinical intervention to maintain homeostasis. Current clinical thinking is comparable to that of cardiology a few decades ago: identification of those at risk, use of accurate measures to report function/dysfunction, and introduction of new acute management and secondary preventative interventions.

Current treatment options for OA are palliative, with the focus on living well, prolonging joint lifespan, maximising function, and improving quality of life. NICE recommend the use of supportive measures, such as education, exercise, and weight loss, supported by analgesia (including non-steroidal and steroidal anti-inflammatories), physiotherapy, and surgery when the joint organ has failed.[6] Exercise rehabilitation offers benefits for symptoms, BMI, and modulation of inflammation and should include cardiovascular, open and closed kinetic chain, neuromuscular control, mobility, and joint muscle specific plyometrics.[11]

Recent guidance also recommends the use of primary, secondary, and tertiary prevention to improve knee health with common themes which can be mapped across to other joints (Figure 1).[7,11] The OPTIKNEE initiative aims to provide consensus on OA secondary prevention options prior to symptomatic or functional problems, with the authors stating that this should be seen as a 'call to action' for MSKI clinicians and researchers.[11] Their recommendations focus on a 'whole lifespan approach' to improve joint global health using a patient-centred approach (Table 2) – an approach mirrored by UK Defence Rehabilitation, who are tasked to deliver occupationally-focused rehabilitation and return individuals to full function and operational deployment.[1]

Clinical recommendations	Research recommendations
Prioritise single and multi-structure injuries which fail to respond as expected or have subsequent injury	Prioritise symptomatic over radiographic osteoarthritis, and understand the influence of the social determinants of health
Create person-centred interventions to mitigate modifiable risk factors, inc. education, self-management and exercise. These should start early and continue for lifespan	Studies should include a range of pathologies with risk and rehabilitation outcomes monitored for five years or more
Acute injury management should centre on education, with initially supervised and progressive, patient-centred rehabilitation. Programmes should include a variety of	Monitor pain, adverse events, quality of life, cognitive behavioural factors, function, strength, activity participation and a global assessment. Standardisation of outcome measures used.

exercises and prioritise return to activity, engagement and self-management.	
Monitor pain, adverse events, quality of life, cognitive behavioural factors, function, strength and activity participation	

Table 2. OPTIKNEE clinical and research recommendations to knee health promotion and post-traumatic OA prevention. Adapted from 'OPTIKNEE 2022: consensus recommendations to optimise knee health after traumatic knee injury to prevent osteoarthritis'[11]

Beyond analgesia, there are no effective pharmacological interventions for OA, however there is a renewed focus on the development of disease-modifying anti-osteoarthritis drugs (DMAODs).[23] These have proven difficult and costly to develop, in part due to study population selection, given that OA has a heterogenous population who respond differently depending on endotype and phenotype, and lack of consensus regarding outcome measures to monitor response.[23-25]

Directions of Further Research

The current key research priorities are to understand pathophysiological mechanisms, earlier recognition and diagnosis, and optimisation of prevention and management strategies (particularly relevant for PTOA, as the index trauma should initiate preventative interventions).[7,10-11,25]

A particular challenge in the research, and clinical, fields relate to the significant discordance between imaging (radiographic or structural OA), knee pain (symptomatic OA), and a physician-diagnosed OA, a result of the poorly understood interactions between risk and individual factors (Figure 1). A recent US military study showed less than half of those with radiological OA reported symptoms.[10] Another way to frame this discordance is to describe either the OA *disease* (underlying pathophysiology and cellular biology) or the OA *illness* (an individual's feeling or experience, characterised by symptoms, function and quality of life).[11] Regardless of terminology used, this phenomenon has implications for the design of clinical research studies, understanding pathways and markers associated with disability, dysfunction and pain, as well as future OA diagnostic criteria.

OA Biomarkers

An area of particular interest, cutting across all the OA research themes, is the use of biological markers, or biomarkers (products created during a pathological process), and their use to diagnose diseases, stratify treatment, monitor disease progression, predict treatment response, and evaluate the effectiveness of new therapies. Specific pathological changes in cartilage, bone and synovium, and concurrent inflammatory and metabolic responses, can be indirectly measured, allowing the identification of homogeneous subgroups/phenotypes based on shared clinical, epidemiological, and biochemical characteristics.[20,23] All of these measures are components of a continuum extending from genome proximity to a clinical phenotype of a painful joint limiting function.

Biomarkers can be divided into wet (serum, plasma, urine, or synovial fluid) or dry (ultrasound scanning, USS, or magnetic resonance imaging, MRI), or defined by their role using the BIPEDS classification (burden of disease, investigative, prognostic, efficacy of intervention, diagnostic and safety).[25] Biomarkers can be used to provide an early signal of joint changes, demonstrate specific mechanisms (such as inflammation, boundary lubrication, and changes in glucose metabolism), and judge the impact of management (including diet, exercise or DMOARD development) (Figure 1). Most current serum biomarkers demonstrate ongoing catabolism or anabolism of cartilage and collagen or measure active local inflammation (Table 3), and therefore can identify pathological processes before any symptomatic, structural, or functional impact. This makes them ideal for use in identifying those at high risk who need prevention or active intervention, and to measure the effect of those interventions.

Biological marker name	Pathological mechanisms or associations
Type II collagen pro-peptide (CPII)	Cartilage turnover and synthesis
Cartilage oligomeric matrix protein (COMP)	Cartilage breakdown, osteophyte development
C-terminal telopeptide of collagen type II (CTX-II)	Collagen type II degradation, bone resorption and osteophyte development
Fragment of type III collagen degradation (C3M)	Radiographic changes, positive associations with weight loss and exercise.
Serum fragment of aggrecan (ARGS)	Disease severity, response to exercise
Hyaluronic acid (HA)	Osteophyte development, synovitis
Matrix metalloproteinase 3 (MMP-3)	Proteolytic enzyme, collagen degradation, remodelling
Interleukin 6 (IL-6)	Pro-inflammatory cytokine, inflammatory mediator

Metabolites of C-reactive protein (CRPM)	Inflammatory derivative, radiographic changes, function, positive associations with weight loss and exercise.
Leptin	Pro-inflammatory influence, disease severity, mediates obesity and osteoarthritis association

Table 3. Validated serum osteoarthritis biomarkers and their associated pathological process

Imaging biomarkers, including XR, USS and MRI, can be used to monitor joint recovery following significant trauma. X-ray determines the presence and severity of OA by identifying osteophytes and the degree of joint space narrowing, and are no longer used for diagnosis, but continue to be used for prognostication and research. Unlike XR, USS enables the assessment of active changes and monitoring of joint irritation, recovery, and OA development by reliably monitoring synovitis and synovial thickening.[26] In addition, MRI allows both sequential and functional imaging to assess, in great detail, the changes related to OA development in different joint components.[27]

Genotypes, Phenotypes, and Endotypes

The use of genotyping, phenotyping and endotyping has been suggested to categorise OA sub-groups and target appropriate investigations and interventions (Table 2).[23] Currently, this remains crude, with categories such as Primary (or idiopathic) and Secondary, such as PTOA.

Understanding the underlying genotype allows specific mechanisms to be targeted. A recent study discovered that common polymorphisms in ALDH1A2, which encode the key enzyme for all-trans retinoic acid synthesis, are associated with severe OA, and that in this group, responses to injury were reversed using talarozole, a retinoic acid metabolism blocking agent.[28] This is a good example of the translation of a genetic mechanism and relationship with cartilage injury and inflammation into a tangible treatment model.

Identification of phenotypes and endotypes using biomarkers would also allow targeted recruitment into trials, focussing on treatment-responders, specific interventions which centre on symptoms, such as pain or stiffness, or more aggressive management of those who have a quickly progressive phenotype. The identification of intermediate phenotypes that could parse the heterogeneous population of patients with PTOA into subgroups with more homogeneous treatment responses could aid the development of a 10-year risk model like current osteoporosis management. There is also a potential role for artificial intelligence and machine learning in the prediction of phenotype response to treatment.

Due to the different OA trajectories, with individuals with varied phenotypes progressing and responding to interventions in varied ways, consensus needs to be drawn on which standardised outcome measures to use.[11,25] These should involve both subjective patient-reported outcomes measures (PROMs) to record symptoms and function, and objective markers, including functional measures such as strength or mobility assessments, and imaging, to assess structural changes. This would hopefully mitigate the challenges associated with OA 'illness' v 'disease'. Furthermore, the increasing use of biomarkers makes translation of the endotypes and phenotypes into therapeutic studies feasible, allowing the recruitment of homogenous study populations to improve responsivity and enable meta-analyses.[24]

DMS current and future research studies

OA research is a priority within the Armed Forces, both in the UK and internationally.[4,15] Within the Academic Department of Military Rehabilitation (ADMR), there are multiple studies focused on prevalence, mechanisms and biomarkers, and management.

The Armed Services Trauma and Rehabilitation Outcome (ADVANCE) study is a 20-year cohort study of 579 male combat casualties and 566 matched participants comparing medical and psychosocial outcomes of military personnel exposed and not exposed to significant combat related trauma.[29] The presence of OA will be assessed using knee and hip radiographs, with the impact measured using functional tests such as the 6 metre walk test and PROMs related to pain and function. The baseline analysis results are expected in early 2023 and will allow a greater understanding of the prevalence of OA in injured and non-injured individuals, thereby understanding the risk of military service on developing OA, the risk of traumatic injury on developing PTOA, and the identification and impact of specific OA risk factors like injury type and severity. This cohort will enable sub-group analysis of individuals who underwent traumatic lower limb amputation, and the implications of combat associated amputations on OA, and impact of combat related knee injuries on OA. Furthermore, this analysis will investigate those who were injured but had neither a lower limb amputation or knee injury, to explore whether systemic combat-related trauma (e.g., blast) increases OA risk without local trauma.

Using the same population, the Biomarkers and Joint pain in Military Osteoarthritis (BioMilOA) study aims to understand the role of serum biomarkers, both presence and change of, between

those with and without radiographic PTOA and investigate their predictive value for incidence of, and worsening over time, of radiographic OA, joint pain, and function. This study, a collaboration between ADVANCE and the University of Nottingham, will allow the role of biomarkers to be better understood in a large military population, laying the foundations for targeted surveillance and intervention, and providing a unique opportunity to compare baseline and follow-up factors in those with painful and non-painful PTOA and idiopathic OA. Whilst the primary focus will be on those sustaining trauma, it will also provide important data on the utility of biomarkers in a general military population.

The higher rates of OA seen in active populations is believed to be linked to the increased physical activity and greater mechanical joint loading compared with sedentary occupations, but evidence of a causal link remains elusive despite the intuitive appeal of this.[30] There is also a lack of published data reporting the risk-factors for pre-arthritic disorders in military personnel.[31] The recently completed Military Hip Rehabilitation Outcome (MILO) study incorporated a population-based case-control study investigating the risk factors for non-arthritic hip pain in relation to lifelong, cumulative occupational physical workload in UK military personnel to inform the development of targeted prevention programmes.[32]

Finally, potential interventions for secondary and tertiary prevention in the Armed Forces could include physical rehabilitation programmes comprised of neuromuscular training, strength and conditioning supported with controlled return to work and appropriate medical grading, optimisation of nutritional status or possible orthoses.[4,11,32] The MILO research programme also included a large, clinical randomised controlled trial aiming to improve the management of intra-articular hip pain by modifying adverse hip joint forces through hip muscle strengthening, restoration of function and activity modification in UK military personnel with hip pain to demonstrate the effect of this in service personnel. These interventions are summarised in Table 4. The results of both the MILO programme case-control study and RCT are due in 2023.

Treatment modality	Treatment content	Treatment goals	Frequency per week (duration)
Group exercise	Strengthening exercises, active range of motion exercises, functional balance drills, gait drills, progressive co-ordination drills, non-weight-bearing aerobic/endurance exercise, and minor team games.	Restore strength of deep hip stabilisers, improve core strength, increase joint range of motion, improve balance and neuro-motor control, improve muscle endurance, and promote group cohesion and social support.	12 (30-45 min)
Individual physiotherapy*	Manual therapy techniques, muscle activation and timing patterns, active and passive range of motion exercises, advice on home-exercise, gait re-education training.	Improve quality and timing of movement, improve muscle strength, reduce pain, increase joint range of motion, induce relaxation, promote normal walking gait.	5 (30 min)
Hydrotherapy/ swimming	Non-weight-bearing aerobic exercise, strengthening exercises, active range of motion exercises, self-paced recreational swimming, progressive/assisted weight-bearing exercise and activity.	Improve muscle strength, improve aerobic capacity, increase joint range of motion, improve confidence in weight-bearing, induce relaxation, and promote enjoyment and variety of treatment.	3 (60 min)
Individual occupational therapy†	Relaxation techniques, postural re-education, cognitive behavioural therapy (CBT) techniques, self-help coping strategies, pain management.	Induce relaxation, promote behavioural change, control pain, correct/improve poor posture.	3 (60 min)
Patient education	Coping with pain, benefits of exercise, joint protection, anatomy and pathology of hip pain, nutrition.	Activity modification, reduction of pain, promotes behavioural change, weight management, improve knowledge of treatment options, and improve ability to relax, improve knowledge of self-help techniques.	2 (60 min)
*Exercise dosage, progression and intensity will be governed by the physiotherapist and tailored to the needs of each individual patient; †Occupational therapy referrals will be individually prescribed to selected patients.			

Table 4 : Components of treatment for residential rehabilitation intervention

Conclusion

The understanding of OA has undergone a revolution in the past two decades. Military service personnel are at increased risk of this disabling condition and its sequelae, and there is a corresponding clinical and research focus within the DMS with the ADVANCE, BioMilOA and MILO studies. Understanding the specific molecular mechanisms underlying the high prevalence of OA in the military will enable the development of strategies to reduce the burden of OA among those serving. Moreover, the use of biomarkers, both following injury and longitudinally, offers the opportunity to risk-stratify and phenotype both injured and non-injured individuals to optimise preventative strategies. The current priority for clinical care is early identification, with the correct and timely use of supportive measures, focussed on symptomatic, not structural, OA, offering the opportunity to prevent or slow progression and therefore minimise subsequent morbidity, loss of function and years lived with disability. It is hoped that this paper will raise awareness of the presence and impact of OA, the available management options, and the future directions of DMS research.

Words: 2996

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