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Position paper

Aarhus Regenerative Orthopaedics Symposium (AROS)

Regeneration in the ageing population

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Abstract — The combination of modern interventional and preventive medicine has led to an epidemic of ageing. While this phenomenon is a positive consequence of an improved lifestyle and achievements in a society, the longer life expectancy is often accompanied by decline in quality of life due to musculoskeletal pain and disability.

The Aarhus Regenerative Orthopaedics Symposium (AROS) 2015 was motivated by the need to address regenerative challenges in an ageing population by engaging clinicians, basic scientists, and engineers. In this position paper, we review our contemporary understanding of societal, patient-related, and basic science-related challenges in order to provide a reasoned roadmap for the future to deal with this compelling and urgent healthcare problem.

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The world population is ageing. Many nations are experiencing an epidemic of ageing due to reduced fertility rates and longer life expectancy (WHO 2011). Western societies have already experienced a major transition in the population age distribution, and now the most profound ageing is being seen in the developing countries. Currently, China—the country with the largest population (1.4 billion)—is transforming into an ageing nation with 400 million people over 65 years old expected by 2050 (Zeng 2012).

Although a substantially greater percentage of the world's population is living longer, many people are doing so with a reduced quality of life due to disability and pain from musculoskeletal tissue degeneration, which results in debilitating conditions. The sequelae of the ageing epidemic have thus brought into clearer focus the need to: (1) gain a better understanding

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of the cause of age-related musculoskeletal tissue degeneration; (2) formulate strategies involving changes in lifestyle, physiotherapy protocols, and/or therapeutics to ameliorate the processes underlying this degeneration; and (3) develop regenerative treatments that could apply to ageing individuals. Regenerative orthopedics deals with restoring the body's native musculoskeletal tissues following traumatic or degenerative damage. Orthopedic surgery has—perhaps somewhat inconspicuously—been at the forefront of regenerative treatment strategies dating back to the discovery of the osteoinductive properties of demineralized bone matrix (DBM) with its bone morphogenetic proteins (BMPs) by Marshall R. Urist in 1965 (Urist 1965), and subsequent purification and characterization of BMPs in the late 1980s (Wozney et al. 1988, Luyten et al. 1989). This was followed by cell-based treatments such as autologous chondrocyte implantation (ACI) in 1994 (Brittberg et al. 1994), and more recently the use of mesenchymal stem cells (MSCs) for treatment of cartilage lesions (Nejadnik et al. 2010, Wong et al. 2013).

The Aarhus Regenerative Orthopaedics Symposium (AROS) 2015 involved an interdisciplinary group of basic scientists and clinicians working with orthopedic regenerative treatments. The goal was to review our contemporary understanding of issues related to orthopedic regeneration in an ageing population in order to provide a reasoned roadmap for the future to deal with this healthcare problem. A previous journal issue of articles collected into a "symposium" in 2004 addressed the orthopedic challenges to be met in dealing with the ageing epidemic (Strauss 2004). AROS was organized to bring this problem into a clearer, contemporary light. This position paper is accompanied by 4 review papers on selected topics related to our current understanding of (1) the underlying causes of age-related musculoskeletal tissue degeneration with comments on the most promising targets for the amelioration of the degenerative processes, and (2) the prospects and promise of regenerative orthopedics in an ageing population.

Regenerative challenges in the ageing population

What is an older or elderly person? Developed countries have generally accepted having reached the age of 65 years as a definition (WHO 2016). From cellular, physiological, and mental standpoints, however, an exact definition becomes inaccurate and debatable. The exact mechanisms of cellular ageing are generally unknown, but they have been shown to include telomere shortening, increased DNA methylation, heightened oxidative stress and inflammation, and changes in mTOR-regulated autophagy. Some of the underlying mechanisms of cellular ageing for specific musculoskeletal tissues are discussed in selected review papers in this special issue. We have divided the challenges that have been identified into 3 themes: societal, patient-related, and basic science-related, in order to describe the issues and associated challenges.

Societal challenges

Rising healthcare expenditure has already proven to be an important topic on the political agenda, mainly due to the demographic shift in age distribution and development of new treatments. Furthermore, the lack of proportional relationships between public health and associated costs calls for an increased focus on cost-effectiveness. The use of ACI for the treatment of focal cartilage lesions in the knee is a recent example of a validated treatment with good long-term clinical follow-up data that is unavailable in many countries due to the high cost of in vitro cell expansion (Clar et al. 2005). As a consequence, the use of minced autologous cartilage chips embedded in fibrin glue has been developed as a potential cost-effective alternative for some of these patients (Christensen et al. 2015). Scientists in regenerative medicine have traditionally (and for good reasons) focused on novel and advanced technologies in the hope of breakthrough discoveries (Toh et al. 2014). The growing market for off-the-shelf tissue-engineering products and banked cells and tissues is driving innovations in regenerative orthopedics. However, a more pragmatic approach is to include early considerations of the potential cost to the end-user, as this dictates the magnitude of clinical use. Hence, true scientific novelty in the development of regenerative therapies in orthopaedics may be the combination of technology and its applicability for translation into societal and clinical use.

In healthcare expenditure prioritization, a focus on prevention versus disease treatment has shown importance, especially in cardiovascular medicine and endocrinology—with several successful examples including: statins; anticoagulants; and control of blood sugar level through exercise, dietary restrictions, and medication.

Patient-related challenges

Outcome measures

Patient-related outcome measures (PROMs) have been used for the evaluation of clinical outcomes in orthopedics for decades, which today are often included in national registries. PROMs address general and disease-specific well-being before, during, and after treatment in order not only to determine whether a treatment works, but also how it works (Greenhalgh et al. 2005). Validation of PROMs is an extensive process. Most questions in PROMs are age-neutral, but questions such as whether you have used a stick or crutch within the last 4 weeks may be more important for an 80-year-old than for a 15-year-old, compared to, for example, the question of whether you are able to squat (Tegner-Lysholm knee-scoring scale). In the evaluation of regenerative treatments or treatments in general, an age-adjusted PROM should weigh up the importance of the questions for the individuals, and this adjustment is possible if validated with modern item response theory (IRT) methods.

Co-morbidity

A Swedish study of 1,099 patients aged 77–100 years showed that hypertension, dementia, and heart failure were the most prevalent chronic diseases at 38%, 21%, and 18%, respectively, and that 55% had multi-morbidity (Marengoni et al. 2008). The systemic and local impact of these conditions on the efficacy of any regenerative treatment is unknown, but should be considered in future studies. Concomitant pulmonary dysfunction, cardiovascular disease, and dementia, and cognitive impairments of many age-related diseases can hinder postoperative rehabilitation, which is an important predictor of outcome in many orthopedic surgical treatments (Shelbourne and Klotz 2006, Mithoefer et al. 2009, Heyes et al. 2015).

The tissue microenvironment is important for the regenerative outcome regardless of approach (reviewed elsewhere: Barthes et al. 2014). Many elderly patients have asymptomatic low-grade chronic inflammation that causes environmental changes at the cellular level, which have been linked to increased incidence of several age-related diseases, including osteoarthritis (Koenig et al. 1999, Duncan et al. 2003). While the effect of inflammation on tissue regeneration is not well understood, its influence on regeneration has begun to be reported. Of note are recent studies suggesting that cytokines involved in inflammation may provide both anabolic and catabolic stimuli, which in the future may be modulated in favor of tissue regeneration (Filbin 2006, Mountziaris and Mikos 2008).

Polypharmacy

The tissue microenvironment is affected by medication. Even when used alone, commonly prescribed drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) are controversial regarding their effects on orthopedic procedures. While the effects of single drugs on regeneration may be evaluated using simple experimental study designs, elderly patients are usually taking several drugs on a regular basis. A review by Hajjar et al. (2007) showed that more than half of the patients aged 65 or more took ≥ 5 medications per day. Another study of 236 patients aged 65 or more in an outpatient clinic showed that 60% were taking medications with suboptimal indications (Lipton et al. 1992). While little is known about drug interactions in polypharmacy and the consequences of these interactions in the specific treatments for which they are prescribed, even less is known about their effects on the tissue-specific microenvironment and regeneration. Polypharmacy or even the use of single drugs may thus be a significant clinical confounder in treatment outcome in this age group.

External validity of clinical trials

Much effort is often put into ensuring the internal validity of a study by providing sufficient statistical power, minimizing the risk of bias, and eliminating potential confounders. In order to ensure a statistically significant difference, strict inclusion/exclusion criteria are often applied. When investigating success of regenerative treatments, initial evaluation of efficacy is most often undertaken in a young and otherwise healthy population. Engen et al. (2010) showed that only 4% of patients with focal cartilage lesions seen in their practice would satisfy the inclusion criteria for all randomized controlled trials performed in articular cartilage repair studies. As a consequence, patients receiving treatment may not match those enrolled in the clinical studies, which ultimately should have been providing guidance on patient selection for a specific treatment. This has been shown with chondrocyte transplantation for repair of focal cartilage lesions (Foldager et al. 2016). This discrepancy in the profiles of patients in clinical trials and in the general treatment population, which may reflect a bias toward early commercial or research successes, is a significant limitation to the external validity of these trials.

Basic science-related challenges

Development and adaptation of animal models of ageing

Because the exact mechanisms of human ageing are poorly understood, the use of animal models in ageing and ageing-related disease studies is important. However, the development and validation of animal models of ageing has several pitfalls. Such animal models for ageing-related diseases in the musculoskeletal system such as osteoporosis, degenerative synovial joint diseases, and intervertebral disc degeneration include: species with spontaneous disease development (Bendele and Hulman 1988); surgical interventions for accelerated disease progression (Glasson et al. 2007, Bendtsen et al. 2011); transgenic mice (Neuhold et al. 2001); and inbred senescence-prone mice (Takeda 1999). While certain species with spontaneous age-related diseases might essentially recapitulate human disease development, the cost and time required mean that such studies are practically non-existent in the literature. In all other animal models, it is important to understand the inherent limitations of each model. For example, in models where surgical manipulation leads to joint instability in the knee, and needle puncture of the intervertebral disc results in degeneration, the outcome is due to an acute inflammatory response and alteration in biomechanics followed by a cascade of local physiological/pathological changes in an otherwise healthy animal; this is different from the chronic ageing-related degenerative processes usually seen in humans. Thus, the impact of accumulated cellular damage due to ageing (which can influence pathogenesis) is unlikely to be recapitulated in these healthy, mechanically insulated animals—and this fact is widely neglected in animal studies.

The systemic approach—rejuvenation

It is important to recognize that ageing is a systemic event, not a local one. In general, regenerative initiatives and therapeu-

tics for ageing diseases are principally informed by joint- and disease-specific mechanisms and may therefore be limited in effectiveness; this reflects the difficulty in dealing with the systemic complexity of ageing. As we are confronted with an epidemic of ageing, it is time to shift from treating local disease to interdisciplinary and combinatorial approaches targeting areas of systemic rejuvenation as a principle for local regeneration, or at least facilitation or acceleration of locally applied regenerative treatments.

Summary

Age-related musculoskeletal tissue degeneration is a complex and complicated problem, which has always been with us. Until 60 years ago, the only way for an individual to deal with the pain and disability of this condition was "to cope", and simply to take pain medication. The advent of therapeutics for the medical management of the disorder (viz. nonsteroidal anti-inflammatory drugs, NSAIDs) and of the surgical treatment in the form of joint replacement, with its immediate pain relief for most patients, transformed the lives of many. However, we now know that long-term administration of NSAIDs comes with its own set of problems, and the limitations in the longevity of prosthetic joints is such that arthroplasty cannot be relied upon to be a stand-alone modality for dealing with the ageing epidemic and the extended lives of older individuals. While drugs and devices have helped us through the past 60 years, it will probably be biologics, in an injectable form, that will be necessary to help us through the next 60 years (Spector and Lim 2016). These therapeutic promises are, however, based on an understanding of the mechanisms underlying age-related degeneration with attention to pathophysiology of the patient as a whole and to the localized diseases. This symposium allowed us to compile a contemporary view of these important issues to help us develop meaningful strategies to provide a more satisfactory quality of life in the epidemic of ageing.

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eSupplementum 363 also comprises the following articles

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