Communication

Elephants, mobility and captivity: what can these mighty and majestic animals teach us about joint health and osteoarthritis?

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Simple Summary: African and Asian elephants are the largest animals that live on land. In order to find fresh food and water they need to be highly mobile and active. Despite their huge size, African elephants are highly mobile and can walk up to 28 km per day, although they usually walk 25 km on a daily basis. Asian elephants walk up to 21 km each day and they can be active for up to 20 hours every day through walking, grazing, swimming and socializing. Mobility helps elephants maintain their joints and muscles. However, many captive-held zoo elephants are kept in small enclosures with hard surfaces (i.e. concrete, tarmac and hard backed dirt), often in very small spaces. Therefore, captive-held elephants cannot exercise freely and as much as wild-living elephants. This makes them more prone to gaining weight, getting obese, becoming lame and developing bone and joint diseases such as arthritis, especially osteoarthritis (OA). Health and welfare problems in captive-held elephant may be caused by the lack of mobility. This communication focuses on the possible link between mobility, captivity and the development of OA in elephants.

Abstract: The African bush and forest elephants, *Loxodonta Africana* and *Loxodonta cyclotis*, and the Asian elephant, *Elephas maximus*, are the largest land-dwelling animals. Elephants need to be highly mobile and active in order to find fresh food and water, and in the case of males, to locate females in estrus for breeding. Asian elephants walk up to 21 km each day and African elephants can walk up to 28 km per day. This high level of mobility in the wild is also important for maintaining an optimum musculoskeletal health. However, most zoo elephants live in restricted spaces and cold climates that require extended periods of indoor confinement are therefore unable to be as physically active. Zoo enclosures for elephants are relatively small with hard surfaces (i.e. concrete, tarmac and hard packed dirt), so they cannot exercise and are forced to stand on unnaturally hard surfaces continually. Physical inactivity in captivity makes them more prone to gaining weight and developing bone and joint diseases such as osteomyelitis, joint ankylosis and osteoarthritis (OA). Many health and welfare problems in captive elephants are likely to be caused by the lack of mobility. This perspective article focuses on the possible link between captivity, mobility, physical inactivity and the development of OA in captive elephants.

Keywords: osteoarthritis; African elephant; Asian elephant; captivity; housing; mobility

1. Introduction

Osteoarthritis (OA) is the most common form of arthritis in the world, the leading cause of disability and the primary source of societal cost in older adult humans [1]. According to the World Health Organization (WHO), OA affects millions of people worldwide ¹. Recent studies suggest that OA affects 7% of the global population, which is more than 500 million people worldwide, with women disproportionately affected by the condition [2], especially after menopause [3–5]. Although OA is primarily related to aging, it is, along with many other forms of chronic disease, also associated with a wide variety of modifiable and non-modifiable risk factors that include: overweight and obesity [6,7], sedentary behavior [8] and lack of physical exercise [9]. In addition to the primary risk factors of aging, obesity, gender, and genetics, other inciting risk factors for OA may include previous joint trauma or history of repetitive joint injuries or even the presence of metabolic syndrome and endocrine disease [10]. However, the disease is primarily biomechanical. There are biomechanical [11–13], inflammatory [14–16], metabolic [17] and nutritional [18–20] factors that have been demonstrated to play dominant roles in the initiation and progression of OA.

2. Mobility and the evolution and migration of modern Homo sapiens

Mobility was essential for the evolution of Homo sapiens and an essential component of the "Global Human Journey" [21,22]. Humans evolved from an ancestor that was not limited to trees or other elevated habitats. Our human ancestors were highly mobile and agile, which was essential for gathering food and finding new shelter [23]. The ability to move and migrate allowed them to colonize the entire planet and settle on every continent [24]. Now that we have colonized and dominated every corner of the globe we face a new set of challenges. The rising global burden musculoskeletal (MSK) diseases is now threatening one of the key the human qualities that allowed us to become the dominant species: mobility. The recent Global Burden of Disease (GBD) Study estimated the burden disability in 187 countries and 21 regions of the world for the years 1990, 2010 and 2013 of all MSK disorders. OA rheumatoid arthritis (RA), gout, low back pain (LBP), neck pain (NP) and all other MSK disorders combined caused 21.3% of the total years lived with disability (YLDs) globally [25,26]. MSK health is critical for human function, enabling mobility, dexterity and the ability to work and actively participate in all aspects of life [27]. Global MSK health targets should also be set to reflect maintenance of mobility, participation and physical function as key components of functional ability and performance [28].

3. What can we learn about joint health and OA from the African elephant *Loxodonta Africana* and the Asian elephant *Elephas maximus*?

Much of what we know about osteoarthritis comes from epidemiological studies [29–32], especially studies that were conducted in large cohorts such as the Framingham Study [33,34]. Many investigators have designed and conducted clinical trials to examine the effects of physical activity and inactivity on synovial joint health and OA symptoms, focusing on humans as the primary target population [35]. However, there is a great deal that we can learn from large animals. Elephants are the largest land-dwelling mammal. They have evolved a specialized foot morphology to help reduce locomotor pressures while supporting their large body mass [36]. Elephant limbs display unique morphological features which are related mainly to supporting their enormous body weight and the knee joint plays crucially important roles in weight bearing and locomotion [37]. They are not perhaps the largest land dwelling mammals that roamed the Earth; the woolly mammoth (*Mammuthus primigenius*), *Deinotherium* and *Palaeoloxodon namadicus* were the largest known mammals to walk on the planet.

¹ https://www.who.int/medicines/areas/priority_medicines/Ch6_12Osteo.pdf

4. Mobility

Elephants and their ancestors were designed to be highly mobile mammals, enabling them to migrate and expand their territory [38]. Wild modern elephants need to be highly mobile to find fresh food and water, and this mobility helps them survive and maintain optimal musculoskeletal health. Despite their massive size, African elephants are highly mobile and can walk up to 28 km per day, which creates exciting opportunities for research on gait and kinematics of locomotion in these animals [39]. Asian elephants walk up to 21 km each day and they can be active for up to 20 hours every day through walking, grazing, swimming and socializing. African elephants need to be mobile and find water source to rehydrate themselves. However, recent research suggests that captive elephants can only walk up to a maximum of 5 km per day [40]. Holdgate et al., who did this work have proposed that distance walked is not related to health or behavioral outcomes including foot health, joint health, body condition, although their studies do not compare captive and wild elephant populations [40].

4. Housing, Husbandry and Management

An important consideration is the overall housing, husbandry and management of captive elephants and the size of environments and enclosures in which they are kept. Captive elephants experience a number of health issues that can contribute to their overall well-being and survival and it known that housing [41]., husbandry [42] and management [43] are important for their welfare. Elephants kept in captivity should be managed by employing the best practices aimed at meeting their welfare needs (i.e. physical, physiological and psychological) to ensure healthy, sustainable populations [44].

This is an under-researched area, especially in relation to the development of lameness and OA in captive elephants. However, most zoo elephants are kept in enclosures with hard surfaces (i.e. concrete, tarmac and hard packed dirt) and small spaces and they cannot exercise as much as wild animals [45]. This raises important questions for the management of these animals, highlighting the crucially important areas of stress, obesity and poor adult survivorship among captive elephants [44,45]. Captivity makes elephants more prone to gaining weight and developing diseases such as osteomyelitis, joint ankylosis and OA.

In elephants age is the primary contributing factor in the pathogenesis of foot pathology [46] and joint diseases such as OA [47]. After age, obesity and adiposity are important risk factors for the development of OA in humans and animals [48–50]. Given that increasing age and obesity are major risk factors for the development of human OA, closer examination of captive animals is likely to contribute to a broader comparative understanding of OA development across a number of mammalian species, including elephants [29,51]. Therefore, captive elephants can teach us a great deal about the link between mobility, captivity and the development of OA associated with sedentary behavior. In fact, it could be argued that the captive elephant is a perfect large animal model for the studying the link between sedentarism, lack of mobility, osteoarthritis and the co-morbidities that are commonly associated with osteoarthritis [52]. For many decades OA was considered to be a wear and tear disease but recent research suggests that OA has important metabolic and inflammatory components [16,17,53,54].







Figure 1. Asian elephants in the wild (top panel) and in captivity with limited space (middle panel). African elephants with more space in a reserve (bottom panel).

In humans obesity and lack of physical activity are major contributors to the development of OA [33]. However, there is no convincing published evidence in humans that walking and running contributes to OA [55][56]. Therefore, it is hardly surprising that captive elephants suffer from lameness and OA as they have to stand for long periods of time on hard surfaces and they are unable to exercise enough and walk the normal distances that they would in the wild every day. They cannot be active in very cold climates and in small zoo enclosures where their freedom and mobility is highly restricted. These are important ethical and welfare considerations that must be taken into account in future captivity and conservation programs.

There are currently no effective drugs and pharmacological treatments for OA [57]. Recent clinical research suggests that weight loss, physical activity and increasing muscle mass and strength are the only effective strategies for reducing pain and enhancing mobility in subjects with OA [58]. The only way to slow down the pain and progression of OA appears to be physical exercise, avoiding obesity and maintaining a healthy weight [59–62]. Non-steroidal anti-inflammatory drugs (NSAIDs) can only treat the symptoms of OA. Studies have examined the pharmacokinetics of orally administered phenylbutazone in African and Asian elephants and the evidence suggests that different treatment regimens should be used for each species, based on size and weight [63]. Similar studies have established the optimal dosage for using ketoprofen [64] and ibuprofen [65] in elephants. However, these NSAIDs can be highly toxic to the gastrointestinal tract in humans and in large animals such as horses and elephants, causing general toxicity, colitis and inhibition of mucosal barrier healing [66].

Cellular senescence is a state of irreversible growth arrest triggered by various stressors [67]. In synovial joints the process of chondrosenescence is an important contributor to OA progression [68– 70]. A deeper understanding of the molecular mechanisms underlying the multi-step progression of senescence may lead to the development of new therapeutic strategies for age-related pathologies [71], such as OA. A recent systematic review of the published literature on studies of the senolytic effects of exercise and physical activity on senescent cells under various states in both human and animal models suggests that exercise has senolytic properties [72]. This may explain the beneficial impacts that patients with OA see when they exercise. Therefore, one possible and achievable strategy currently available to slow OA progression in elephants is to allow them to exercise and walk more and to look after their feet by limiting walking on unnaturally hard surfaces. It is vitally important that more exercise should be recommended for captive elephants, and hopefully this paper will contribute to the development of future guidelines and white papers to support the development of better welfare for captive animals. Zoo elephants will need to get as much space as possible (with softer surfaces) to move and exercise freely but dietary supplementation may also be necessary. There is no solid research in this area and most of the evidence is anecdotal and provided by wildlife and zoo veterinarians. Meanwhile, OA researchers are looking for new therapies for this disease in humans and non-human animal models and all the evidence from captive elephants suggests that captivity and reduced physical activity can accelerate the development of OA. Therefore, the physical activity that has been recommended for human patients with OA can also be recommended for elephants, who need it as much as we do.

5. Conclusions

Physical inactivity and sedentary behavior contribute to poor health in humans. Captivity and reduced mobility are also major contributors to poor health in captive animals, including elephants. Wild elephants are highly mobile and require the freedom and space to reach their daily activity goals, often called "lumbering". Elephants in small enclosures in zoos do not get enough exercise compared to their counterparts in the wild. Elephants in Safari parks and sanctuaries may have more freedom to move around but unless they live in reserves and national parks, they do not have enough space and opportunities for "lumbering" or "hurtling" the long distances that they were evolutionary designed for. Captive elephants have a shorter lifespan. Keeping them in captivity may protect them

from poaching but the protection afforded to them presents a whole new set of health challenges, including overweight, obesity, lameness and OA. Several years ago the American Zoological Association (AZA) published research proposing that captive Asians live on average 44 years. They also claimed wild Asian elephants live about the same length of time. However, from our experience there is a problem with this claim pertaining to wild elephants. There are no long-term studies of wild Asian elephants to support such a claim. However, there is much information about captive elephants living into their 80's all over Asia. The reason the captive elephants in Asia live much longer than the captive elephants in the Western world is due to climate and management. In Asia, until very recently, captive elephants lived in the jungles and worked in the lumber industry. They did not live on hard surfaces, they were fed a natural diet, they got plenty of exercise and usually were with conspecifics. More recently, as the captive-held elephant in Asia has been brought out of the jungle and into cities for tourist entertainment, their health has suffered, disease is prevalent, and lives are shorter. In conclusion, elephants confined in small spaces without adequate exercise, living on unnaturally hard surfaces suffer from musculoskeletal disease and pain and consequently die early.

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References

- 1. Hunter, D. J.; Bierma-Zeinstra, S. Osteoarthritis. *Lancet* **2019**, *393*, 1745–1759.
- 2. Hunter, D. J.; March, L.; Chew, M. Osteoarthritis in 2020 and beyond: a Lancet Commission. *Lancet* **2020**, *396*, 1711–1712.
- 3. Hanna, F. S.; Wluka, A. E.; Bell, R. J.; Davis, S. R.; Cicuttini, F. M. Osteoarthritis and the postmenopausal woman: Epidemiological, magnetic resonance imaging, and radiological findings. *Semin. Arthritis Rheum.* **2004**, *34*, 631–636.
- 4. Karsdal, M. A.; Bay-Jensen, A. C.; Henriksen, K.; Christiansen, C. The pathogenesis of osteoarthritis involves bone, cartilage and synovial inflammation: may estrogen be a magic bullet? *Menopause Int* **2012**, *18*, 139–146.
- 5. Stevenson, J. C. A woman's journey through the reproductive, transitional and postmenopausal periods of life: impact on cardiovascular and musculo-skeletal risk and the role of estrogen replacement. *Maturitas* **2011**, *70*, 197–205.
- 6. Felson, D. T. Weight and osteoarthritis. Am. J. Clin. Nutr. 1996, 63, 430S-432S.

- 7. Zhang, Y.; Jordan, J. M. Epidemiology of osteoarthritis. *Clin Geriatr Med* **2010**, *26*, 355–369.
- 8. Blüher, M. Obesity: global epidemiology and pathogenesis. *Nat. Rev. Endocrinol.* **2019**, *15*, 288–298.
- 9. Booth, F. W.; Roberts, C. K.; Laye, M. J. Lack of exercise is a major cause of chronic diseases. *Compr. Physiol.* **2012**, *2*, 1143–1211.
- 10. Felson, D. T. Risk factors for osteoarthritis: understanding joint vulnerability. *Clin. Orthop. Relat. Res.* **2004**, S16-21.
- 11. Englund, M. The role of biomechanics in the initiation and progression of OA of the knee. *Best Pract Res Clin Rheumatol* **2010**, *24*, 39–46.
- 12. Andriacchi, T. P.; Mündermann, A. The role of ambulatory mechanics in the initiation and progression of knee osteoarthritis. *Curr. Opin. Rheumatol.* **2006**, *18*, 514–518.
- 13. Pandy, M. G.; Andriacchi, T. P. Muscle and joint function in human locomotion. *Annu. Rev. Biomed. Eng.* **2010**, *12*, 401–433.
- 14. Berenbaum, F. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). *Osteoarthr. Cartil.* **2013**, *21*, 16–21.
- 15. Berenbaum, F.; Walker, C. Osteoarthritis and inflammation: a serious disease with overlapping phenotypic patterns. *Postgrad. Med.* **2020**, *132*, 377–384.
- 16. Sellam, J.; Berenbaum, F. Is osteoarthritis a metabolic disease? *Joint Bone Spine* **2013**, 80, 568–573.
- 17. Mobasheri, A.; Rayman, M. P.; Gualillo, O.; Sellam, J.; van der Kraan, P.; Fearon, U. The role of metabolism in the pathogenesis of osteoarthritis. *Nat. Rev. Rheumatol.* **2017**, *13*, 302–311.
- 18. Thomas, S.; Browne, H.; Mobasheri, A.; Rayman, M. P. What is the evidence for a role for diet and nutrition in osteoarthritis? *Rheumatology* **2018**, *57*, iv61-iv74.
- 19. Musumeci, G.; Mobasheri, A.; Trovato, F. M.; Szychlinska, M. A.; Imbesi, R.; Castrogiovanni, P. Post-operative rehabilitation and nutrition in osteoarthritis. [version 3; peer review: 2 approved, 1 approved with reservations]. *F1000Res.* **2014**, *3*, 116.
- 20. Szychlinska, M. A.; Di Rosa, M.; Castorina, A.; Mobasheri, A.; Musumeci, G. A correlation between intestinal microbiota dysbiosis and osteoarthritis. *Heliyon* **2019**, *5*, e01134.
- 21. Stringer, C.; McKie, R. African exodus: The origins of modern humanity. 1998.
- 22. Harari, Y. N. Sapiens: A brief history of humankind. **2014**.
- 23. Lieberman, D. E. The story of the human body: evolution, health and disease. *Fam Med* **2016**, *48*, 822–823.
- 24. Bellwood, P. First migrants: ancient migration in global perspective. **2014**.
- 25. Smith, E.; Hoy, D. G.; Cross, M.; Vos, T.; Naghavi, M.; Buchbinder, R.; Woolf, A. D.; March, L. The global burden of other musculoskeletal disorders: estimates from the Global Burden of Disease 2010 study. *Ann. Rheum. Dis.* **2014**, *73*, 1462–1469.
- 26. Woolf, A. D. Global burden of osteoarthritis and musculoskeletal diseases. *BMC Musculoskelet. Disord.* **2015**, *16*.
- 27. Briggs, A. M.; Cross, M. J.; Hoy, D. G.; Sànchez-Riera, L.; Blyth, F. M.; Woolf, A. D.;

- March, L. Musculoskeletal health conditions represent a global threat to healthy aging: A report for the 2015 world health organization world report on ageing and health. *Gerontologist* **2016**, *56 Suppl* 2, S243-55.
- 28. Milte, R.; Crotty, M. Musculoskeletal health, frailty and functional decline. *Best Pract Res Clin Rheumatol* **2014**, 28, 395–410.
- 29. Felson, D. T. Epidemiology of hip and knee osteoarthritis. *Epidemiol Rev* **1988**, *10*, 1–28.
- 30. Hochberg, M. C. Epidemiology and genetics of osteoarthritis. *Curr. Opin. Rheumatol.* **1991**, *3*, 662–668.
- 31. Neogi, T.; Zhang, Y. Epidemiology of osteoarthritis. *Rheum Dis Clin North Am* **2013**, 39, 1–19.
- 32. Johnson, V. L.; Hunter, D. J. The epidemiology of osteoarthritis. *Best Pract Res Clin Rheumatol* **2014**, 28, 5–15.
- 33. Felson, D. T.; Anderson, J. J.; Naimark, A.; Walker, A. M.; Meenan, R. F. Obesity and knee osteoarthritis. The Framingham Study. *Ann. Intern. Med.* **1988**, *109*, 18–24.
- 34. Zhang, Y.; Niu, J.; Kelly-Hayes, M.; Chaisson, C. E.; Aliabadi, P.; Felson, D. T. Prevalence of symptomatic hand osteoarthritis and its impact on functional status among the elderly: The Framingham Study. *Am. J. Epidemiol.* **2002**, *156*, 1021–1027.
- 35. McAlindon, T. E.; Driban, J. B.; Henrotin, Y.; Hunter, D. J.; Jiang, G. L.; Skou, S. T.; Wang, S.; Schnitzer, T. OARSI Clinical Trials Recommendations: Design, conduct, and reporting of clinical trials for knee osteoarthritis. *Osteoarthr. Cartil.* **2015**, *23*, 747–760.
- 36. Panagiotopoulou, O.; Pataky, T. C.; Day, M.; Hensman, M. C.; Hensman, S.; Hutchinson,
- J. R.; Clemente, C. J. Foot pressure distributions during walking in African elephants (Loxodonta africana). *R. Soc. Open Sci.* **2016**, *3*, 160203.
- 37. Weissengruber, G. E.; Fuss, F. K.; Egger, G.; Stanek, G.; Hittmair, K. M.; Forstenpointner, G. The elephant knee joint: morphological and biomechanical considerations. *J. Anat.* **2006**, *208*, 59–72.
- 38. Purdon, A.; Mole, M. A.; Chase, M. J.; van Aarde, R. J. Partial migration in savanna elephant populations distributed across southern Africa. *Sci. Rep.* **2018**, *8*, 11331.
- 39. Chase, M. J.; Schlossberg, S.; Griffin, C. R.; Bouché, P. J. C.; Djene, S. W.; Elkan, P.
- W.; Ferreira, S.; Grossman, F.; Kohi, E. M.; Landen, K.; Omondi, P.; Peltier, A.; Selier, S.
- A. J.; Sutcliffe, R. Continent-wide survey reveals massive decline in African savannah elephants. *PeerJ* **2016**, *4*, e2354.
- 40. Holdgate, M. R.; Meehan, C. L.; Hogan, J. N.; Miller, L. J.; Soltis, J.; Andrews, J.; Shepherdson, D. J. Walking Behavior of Zoo Elephants: Associations between GPS-Measured Daily Walking Distances and Environmental Factors, Social Factors, and Welfare Indicators. *PLoS One* **2016**, *11*, e0150331.
- 41. Edwards, K. L.; Miller, M. A.; Carlstead, K.; Brown, J. L. Relationships between housing and management factors and clinical health events in elephants in North American zoos. *PLoS One* **2019**, *14*, e0217774.
- 42. Lewis, K. D.; Shepherdson, D. J.; Owens, T. M.; Keele, M. A survey of elephant husbandry and foot health in North American zoos. *Zoo Biol* **2010**, *29*, 221–236.

- 43. Miller, M. A.; Hogan, J. N.; Meehan, C. L. Housing and Demographic Risk Factors Impacting Foot and Musculoskeletal Health in African Elephants [Loxodonta africana] and Asian Elephants [Elephas maximus] in North American Zoos. *PLoS One* **2016**, *11*, e0155223.
- 44. Bansiddhi, P.; Brown, J. L.; Thitaram, C. Welfare assessment and activities of captive elephants in thailand. *Animals (Basel)* **2020**, *10*.
- 45. Clubb, R.; Rowcliffe, M.; Lee, P.; Mar, K. U.; Moss, C.; Mason, G. J. Compromised survivorship in zoo elephants. *Science* **2008**, *322*, 1649.
- 46. Gage, L. J. Treatment of osteomyelitis in elephant feet. In *The Elephant's Foot*; Csuti, B.; Sargent, E. L.; Bechert, U. S., Eds.; Iowa State University Press: Ames, USA, 2000; pp. 117–118.
- 47. *Biology, medicine, and surgery of elephants*; Fowler, M. E.; Mikota, S. K., Eds.; Blackwell Publishing Ltd: Oxford, UK, 2006.
- 48. Sowers, M. R.; Karvonen-Gutierrez, C. A. The evolving role of obesity in knee osteoarthritis. *Curr. Opin. Rheumatol.* **2010**, *22*, 533–537.
- 49. Aspden, R. M. Obesity punches above its weight in osteoarthritis. *Nat. Rev. Rheumatol.* **2011**, *7*, 65–68.
- 50. Griffin, T. M.; Guilak, F. Why is obesity associated with osteoarthritis? Insights from mouse models of obesity. *Biorheology* **2008**, *45*, 387–398.
- 51. Loeser, R. F. Aging processes and the development of osteoarthritis. *Curr. Opin. Rheumatol.* **2013**, 25, 108–113.
- 52. Chan, K. W.; Ngai, H. Y.; Ip, K. K.; Lam, K. H.; Lai, W. W. Co-morbidities of patients with knee osteoarthritis. *Hong Kong Med J* **2009**, *15*, 168–172.
- 53. Thijssen, E.; van Caam, A.; van der Kraan, P. M. Obesity and osteoarthritis, more than just wear and tear: pivotal roles for inflamed adipose tissue and dyslipidaemia in obesity-induced osteoarthritis. *Rheumatology* **2015**, *54*, 588–600.
- 54. van den Bosch, M. H. J. Inflammation in osteoarthritis: is it time to dampen the alarm(in) in this debilitating disease? *Clin. Exp. Immunol.* **2019**, *195*, 153–166.
- 55. Eichner, E. R. Does running cause osteoarthritis? *Phys. Sportsmed.* **1989**, *17*, 147–154.
- 56. Williams, P. T. Effects of running and walking on osteoarthritis and hip replacement risk. *Med. Sci. Sports Exerc.* **2013**, *45*, 1292–1297.
- 57. Ghouri, A.; Conaghan, P. G. Update on novel pharmacological therapies for osteoarthritis. *Ther Adv Musculoskelet Dis* **2019**, *11*, 1759720X19864492.
- 58. Messier, S. P.; Loeser, R. F.; Miller, G. D.; Morgan, T. M.; Rejeski, W. J.; Sevick, M.
- A.; Ettinger, W. H.; Pahor, M.; Williamson, J. D. Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: the arthritis, diet, and activity promotion trial. *Arthritis Rheum.* **2004**, *50*, 1501–1510.
- 59. Bennell, K.; Hinman, R. Exercise as a treatment for osteoarthritis. *Curr. Opin. Rheumatol.* **2005**, *17*, 634–640.
- 60. Bliddal, H.; Leeds, A. R.; Christensen, R. Osteoarthritis, obesity and weight loss: evidence, hypotheses and horizons a scoping review. *Obes. Rev.* **2014**, *15*, 578–586.
- 61. Yu, S. P.; Hunter, D. J. Managing osteoarthritis. *Aust. Prescr.* **2015**, *38*, 115–119.

- 62. Barrow, D. R.; Abbate, L. M.; Paquette, M. R.; Driban, J. B.; Vincent, H. K.; Newman, C.; Messier, S. P.; Ambrose, K. R.; Shultz, S. P. Exercise prescription for weight management in obese adults at risk for osteoarthritis: synthesis from a systematic review. *BMC Musculoskelet*. *Disord*. **2019**, 20, 610.
- 63. Bechert, U.; Christensen, J. M.; Nguyen, C.; Neelkant, R.; Bendas, E. Pharmacokinetics of orally administered phenylbutazone in African and Asian elephants (Loxodonta africana and Elephas maximus). *J. Zoo Wildl. Med.* **2008**, *39*, 188–200.
- 64. Hunter, R. P.; Isaza, R.; Koch, D. E. Oral bioavailability and pharmacokinetic characteristics of ketoprofen enantiomers after oral and intravenous administration in Asian elephants (Elephas maximus). *Am J Vet Res* **2003**, *64*, 109–114.
- 65. Bechert, U.; Christensen, J. M. Pharmacokinetics of orally administered ibuprofen in African and Asian elephants (Loxodonta africana and Elephas maximus). *J. Zoo Wildl. Med.* **2007**, *38*, 258–268.
- 66. Marshall, J. F.; Blikslager, A. T. The effect of nonsteroidal anti-inflammatory drugs on the equine intestine. *Equine Vet. J. Suppl.* **2011**, 140–144.
- 67. Wei, W.; Ji, S. Cellular senescence: Molecular mechanisms and pathogenicity. *J. Cell Physiol.* **2018**, 233, 9121–9135.
- 68. Mobasheri, A.; Matta, C.; Zákány, R.; Musumeci, G. Chondrosenescence: definition, hallmarks and potential role in the pathogenesis of osteoarthritis. *Maturitas* **2015**, *80*, 237–244.
- 69. van der Kraan, P.; Matta, C.; Mobasheri, A. Age-Related Alterations in Signaling Pathways in Articular Chondrocytes: Implications for the Pathogenesis and Progression of Osteoarthritis A Mini-Review. *Gerontology* **2017**, *63*, 29–35.
- 70. Batshon, G.; Elayyan, J.; Qiq, O.; Reich, E.; Ben-Aderet, L.; Kandel, L.; Haze, A.; Steinmeyer, J.; Lefebvre, V.; Zhang, H.; Elisseeff, J.; Henrotin, Y.; Mobasheri, A.; Dvir-Ginzberg, M. Serum NT/CT SIRT1 ratio reflects early osteoarthritis and chondrosenescence. *Ann. Rheum. Dis.* **2020**, *79*, 1370–1380.
- 71. van Deursen, J. M. The role of senescent cells in ageing. *Nature* **2014**, *509*, 439–446.
- 72. Chen, X.-K.; Yi, Z.-N.; Wong, G. T.-C.; Hasan, K. M. M.; Kwan, J. S.-K.; Ma, A. C.-H.; Chang, R. C.-C. Is exercise a senolytic medicine? A systematic review. *Aging Cell* **2020**, e13294.