Q17. Is there a need for better standardization in aging-OA animal studies (e.g. age, housing, diet, and water purification technique -> important from a microbiome perspective)?

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Response/Recommendation: Yes. Environmental factors such as housing and cage conditions, water quality, and diet can alter behavior, metabolic and immune health, often through alterations in the gut microbiome, a critical factor in regulating the development of OA in the context of aging. Moreover, other age-related co-morbidities that coexist in our patients can influence OA in the setting of aging. Given the importance of these variables, they should be more consistently reported and analyzed in age-related OA animal studies.

Strength: Strong

Delegate Vote:

Rationale: OA that develops during aging is associated with distinct systemic influences, including sarcopenia and age-related co-morbidities, that can increase severity of disease [1-3]. Alterations in gut microbiota is an important factor that contributes to age-related morbidity, including functional decline and musculoskeletal disease such as OA [4-8]. Dysbiosis has systemic effects on cellular senescence, immune and metabolic health[9-11], and environmental variables such as housing conditions[12, 13], water quality [14, 15], and diet can alter the microbiome of experimental animals. In preclinical aging studies, this can have a profound influence on outcomes if not carefully considered, as animals are exposed to these variables over extended timeframes. Despite their importance, these factors are inconsistently reported in age-related OA studies. Current guidelines (i.e. ARRIVE[16]) provide a framework for preclinical study design and reporting, but do not specifically address these factors. To answer this, Pubmed literature searches were carried out using search terms of "Osteoarthritis AND aging OR age" in combination with the following: housing, cage conditions, diet, water quality, water acidification, microbiome, sarcopenia, senescence. Irrelevant articles and duplicates were removed and merged with publications suggested by co-authors leading to identification of **98** relevant references, of which **52** were selected for this review.

Aging, the microbiome, and OA: Changes to microbiota with age in humans include reduced diversity of bacterial species, and dysbiotic shifts in dominant phyla and species that can have adverse effects on health. For example, older individuals have been reported to have higher abundance of Bacteroides and Clostridium species, and a lower proportion of Firmicutes, than younger individuals [17]. Similar changes with age have been demonstrated in laboratory rodents[18] and canines[19]. Age-related dysbiosis can drive inflammation and metabolic disruption, contributing to frailty [4], altered bone remodeling [5, 20] and OA [6, 7, 9, 21], and are targetable for OA therapy [22].

Sex: OA is more prevalent in women, particularly as we age. Sexual dimorphism in aging mechanisms including sex-specific microbiota differences have been linked to OA, aging [23] and other conditions [24]. Although research identifying mechanistic differences between OA in males and females has been growing, work specifically on the influence of sex on the microbiome needs to be expanded. Another important area to understand sex as a biological variable is the role of menopause in female aging and musculoskeletal health[25, 26], which requires better standardization for how and when menopause should be induced in mice.

Water quality and variability: Water quality, including purification techniques that may alter or introduce contaminants or affect mineral content, may also affect microbiome composition[27, 28]. For example, acidification can significantly reduce alpha diversity and increase potentially pathogenic Bacteroidetes, Actinobacteria, and Proteobacteria[14, 29]. Water quality has been shown to influence disease risk in models of diabetes [29, 30]. Moreover, both aging and water acidification can alter the Firmicutes:Bateroidetes ratio, which can obscure results. Despite these reports, only a minority of preclinical OA studies report details of water source[15]. As there is significant variation in water treatment across animal research facilities, identifying specific standards could be challenging.

Diet: There is substantial data demonstrating that dietary composition, including overall caloric intake[31], specific macronutrients (fats[32], carbohydrates[33]) and micronutrients (Vitamins[34], minerals[35]), influence OA manifestations in preclinical models. Many of these variables can alter the microbiome [36], and high-fat diets in particular have been shown to alter OA and the microbiome in a sex-dependent manner[32]. Although diet has been shown to influence aging in general [37], data from aging-OA models are only more recently reported[38]. Even standard diets from different commercial sources can vary in their impact on the microbiome[36, 39], making consistency and reporting of specific diets a important for long-term aging studies.

Housing: Aspects of housing, such as cage ventilation and bedding material type[12] can significantly impact the murine gut microbiome. Husbandry practices, including differences in enrichment[40], can influence OA disease severity in PTOA models presumably through effects on activity or stress[41]. As mice are coprophagic, the microbiome of cage mates will begin to resemble each other over time more closely than the microbiome of mice in other cages (cage-effects), confounding effects of genotype or treatment. A recent report demonstrated that reducing the number of mice per cage can mitigate cage-effects, increasing statistical power to detect intervention effects [13]. The expense of increased cage numbers could be offset in long-term studies by reductions in mouse numbers needed, thus also addressing goal of reduction (the 3Rs).

Recommendations

In all preclinical studies, consideration of all relevant animal-level factors (chronologic age/age range, model, species, strain, and sex) should be clearly stated. We recommend consulting the ARRIVE (Animal Research: Reporting In Vivo Experiments) guidelines[16] for study design and reporting validation. This practice will ensure better reproducibility and rigor of research on OA. However, these guidelines do not address all the variables that are critical for aging studies, so additional recommendations are as follows. Given the still sparse literature available to guide specific standardization of these variables, we are recommending **standardization of the COLLECTION and REPORTING of details regarding housing, water quality, and specific diet as well as activity in studies of age-associated OA**.

- **Environmental variables for aging studies:** Report specific diets, water characteristics, housing environments, and keep these consistent over the length of an aging study, to improve reliability and comparability of results across studies. For standard and non-standard diets, the product number should be reported, and for collaborative studies involving multiple animal facilities, these variables should be kept consistent across sites. As our understanding of how these variables influence OA is still rudimentary, studies designed to understand their influence is also a priority. As consistency in water, housing, and feed source are often institution specific, local engagement and collaboration with Veterinary staff is necessary.
- **Co-morbidities:** Studying aging-OA in the setting of cardiometabolic risk factors and common age-related co-morbid conditions when designing studies will improve translational value of preclinical research. For example, studying aging OA in the setting of obesity, hypertension[42], diabetes[43], chronic kidney disease[44] should be a priority for the field. This impacts disease mechanisms, phenotype, and potential interventions[45].
- **Behavior assessments:** Given the morbidity of functional decline with age, restoring function and reducing pain that interferes with function is a primary treatment goal for age-related OA. Thus, more aging studies should incorporate outcomes related to pain[46] and physical function[47] to capture effects of interventions on functional decline. Although specific outcomes measured will depend on the model and the goals of individual studies, a recent "comprehensive functional assessment battery (CFAB)" of tests can be used as a guide to capture age-related decline in physical function in mice[48]. Body composition can also be measured to better understand effects of sarcopenia, fat gain, and skeletal changes which influence functional decline with age[49].
- **Inclusion of alternative animal studies:** Our recommendations focus on small animal models, as there is a notable lack of large animal (dog, horse, pig, sheep, goat, or non-human primate) studies that evaluate the effect of age and the microbiome in naturally occurring or experimentally induced OA[50]. Yet, these models more closely mimic human biomechanical and physiological influences on joint health and drug metabolism, and in the case of non-human primates these species develop OA and other co-morbidities at similar relative rates with aging as in humans [51, 52]. Standardizing the environmental variables mentioned above will be a big challenge in these species, but clinical studies in select species and companion animals may provide more "real-world" evidence for success of novel therapeutics. A better understanding of how to optimally utilize these models to facilitate translation for age-related OA needs further exploration.

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