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# The inadequate reporting of sex in research

APPLYING THE LESSONS FROM COVID-19 TO SPEED UP THE AVAILABILITY OF SEX-BASED DATA



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In an article in this issue of *Bone & Joint Research*, Wang et al<sup>1</sup> report results from a meta-analysis on studies investigating the efficacy of stem cell therapies to treat osteoarthritis (OA) of the knee ("Mesenchymal stem cells - a promising strategy for treating knee osteoarthritis: a meta-analysis"). The results are interesting and suggest that adipose-derived stem cells may be more effective than bone marrow-derived, and that low-dose therapies may result in better outcomes than high-dose therapies. What is also of interest is the limited number of subanalyses that were performed. The authors investigated the effects of stem cell dose and source (both donor site and autologous vs allogenic) but no other patient factors such as age, sex, or ethnicity. This may well be due to the limited way in which the results are reported rather than any lack of questioning on the authors' part.

Even in this age of personalized medicine and big data, the reporting of clinical trials often does not permit further analyses and the researchers themselves rarely disaggregate their data. There has been a growing awareness of the sex research gap for some time, but the obvious gendered and racial effects of coronavirus disease 2019 (COVID-19) have brought awareness of this issue to a much wider audience. Of those countries that disaggregate their data, many report that, although women often constitute the majority of COVID-19 cases, men and those from a black and minority ethnic (BAME) background are more likely to die.<sup>2–4</sup> Social factors are likely to play a large part in these statistics but there is enough evidence to suggest that biology also plays a role: in particular, evidence of sex-related differences in the immune response.<sup>5</sup>

In the field of orthopaedics, a joint workshop report from the American Academy of Orthopaedic Surgeons (AAOS) and the National Institutes of Health (NIH) in 2005 - titled 'Does Sex Matter in Musculoskeletal Health?'<sup>6</sup> - concluded that there was a biological basis for sex differences in injury mechanism, pain, pharmacokinetics, healing, and response to therapies that was not well understood, in part, because no one was looking. Awareness of the sex data gap, and the fact that the majority of therapies are optimized for males based on preclinical studies involving only male animals and Phase I and II trials based on mainly male participants, led the NIH to announce in 2014 that it would require investigators to account for sex as a biological variable in research analysis and design.<sup>7</sup> A move that came almost ten years after the AAOS/NIH report and almost a decade and a half after a landmark report by the USA Institute of Medicine.<sup>8</sup>

Fast forward to 2020 and we are still not routinely investigating sex as a biological variable in medical research, never mind any other patient factor, despite growing evidence that this blind spot leads to poorer outcomes for women. Indeed, the data gap is significant and widespread across all sectors; see Caroline Criado-Perez's award-winning book, *Invisible Women*, for illumination.<sup>9</sup> This issue is overtly of key importance in conditions known to behave differently in different sexes, such as osteoporosis,<sup>10,11</sup> but may also be important in less obvious conditions such as fracture repair.<sup>12</sup> Therefore, sex should be considered across the whole spectrum of musculoskeletal research, whether it is in cell culture

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studies<sup>13,14</sup> or bioengineering studies such as Koh et al.<sup>15</sup> For in vivo studies, the Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines<sup>16</sup> require that the sex of the animal is clearly stated and many studies now do this (for instance recent studies by Morcos et al,<sup>17</sup> Tötting et al,<sup>18</sup> and Hanberg et al<sup>19</sup> all describe the sex of the animals). However, reporting sex and actually including sex as a biological variable are poles apart.

In the Wang et al study, seven trials were included in the meta-analysis. Encouragingly, most were Phase I and II trials that included both male and female participants, yet none of the studies performed sub-analyses or provided disaggregated data. Patient factors were restricted to reporting age, sex, and body mass index (BMI) as baseline characteristics and were not factored into the analysis despite the fact that there is evidence for the effects of all three characteristics on stem cell populations.<sup>20–23</sup> Indeed, the studies were not adequately powered to permit these investigations to meaningfully occur. Similarly, in a comprehensive review of the problems facing stem cell therapies in producing consistent and clinically meaningful results, Levy et al<sup>24</sup> discuss everything from passage number to administration route. Sex, however, was mentioned only in a figure legend as a potential contributor to variance of donor cells and not mentioned at all in relation to the recipient of the therapy. This was in spite of the authors recognizing the importance of the host immune response in realizing a therapeutic effect.

Orthopaedics is a field in which clinicians and researchers are familiar with sex-based differences in disease incidence and presentation. Hopefully, larger and adequately powered studies with disaggregated data will mean we soon also become familiar with therapeutic options based on sex and other patient characteristics.

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## References

1. Wang J, Zhou L, Zhang Y, Huang L, Shi Q. Mesenchymal stem cells - a promising strategy for treating knee osteoarthritis: a meta-analysis. *Bone & Joint Res.* 2020.
2. Global Health 5050. COVID-19 sex-disaggregated data tracker: global health 5050: towards gender equality in global health. 2020. <https://globalhealth5050.org/covid19/sex-disaggregated-data-tracker/> (date last accessed 7/8/2020).
3. ONS. Coronavirus (COVID-19) related deaths by ethnic group, England and Wales: 2 March to 15 May 2020: Office for National Statistics. 2020. <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/articles/coronavirusrelateddeathsbyethnicgroupenglandandwales/2march2020to15may2020> (date last accessed 19/6/2020).
4. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature.* 2020;584(7821):430–436.
5. Scully EP, Haverfield J, Ursin RL, Tannenbaum C, Klein SL. Considering how biological sex impacts immune responses and COVID-19 outcomes. *Nat Rev Immunol.* 2020;20(7):442–447.

6. Tosi LL, Boyan BD, Boskey AL. Does sex matter in musculoskeletal health? the influence of sex and gender on musculoskeletal health. *J Bone Joint Surg Am.* 2005;87-A(7):1631–1647.
7. Clayton JA. Studying both sexes: a guiding principle for biomedicine. *Faseb J.* 2016;30(2):519–524.
8. Wizemann TM, Pardue M-L. *Exploring the biological contributions to human health does sex matter?* Washington (DC): Institute of Medicine (US) Committee on Understanding the Biology of Sex and Gender Differences, 2001.
9. Criado-Perez C. *Invisible women: exposing data bias in a world designed for men.* UK: Penguin Random House, 2020.
10. Peng X, Wu X, Zhang J, Zhang G, Li G, Pan X. The role of CKIP-1 in osteoporosis development and treatment. *Bone Joint Res.* 2018;7(2):173–178.
11. de Quadros VP, Tobar N, Viana LR, Dos Santos RW, Kiyataka PHM, Gomes-Marcondes MCC. The 17 $\beta$ -oestradiol treatment minimizes the adverse effects of protein restriction on bone parameters in ovariectomized Wistar rats: relevance to osteoporosis and the menopause. *Bone Joint Res.* 2019;8(12):573–581.
12. Starlinger J, Kaiser G, Thomas A, Sarahudi K. The impact of nonosteogenic factors on the expression of osteoprotegerin and RANKL during human fracture healing. *Bone Joint Res.* 2019;8(7):349–356.
13. Chiu C-H, Chen P, Yeh W-L, et al. The gelling effect of platelet-rich fibrin matrix when exposed to human tenocytes from the rotator cuff in small-diameter culture wells and the design of a co-culture device to overcome this phenomenon. *Bone Joint Res.* 2019;8(5):216–223.
14. Zhang R-K, Li G-W, Zeng C, et al. Mechanical stress contributes to osteoarthritis development through the activation of transforming growth factor beta 1 (TGF- $\beta$ 1). *Bone Joint Res.* 2018;7(11):587–594.
15. Koh Y-G, Lee J-A, Lee H-Y, Kim H-J, Chung H-S, Kang K-T. Reduction in tibiofemoral conformity in lateral unicompartmental knee arthroplasty is more representative of normal knee kinematics. *Bone Joint Res.* 2019;8(12):593–600.
16. Percie du Sert N, Hurst V, Ahluwalia A, et al. The ARRIVE guidelines 2.0: updated guidelines for reporting animal research. *J Physiol.* 2020.
17. Morcos MW, Al-Jallad H, Li J, et al. Phospho1 is essential for normal bone fracture healing: an animal study. *Bone Joint Res.* 2018;7(6):397–405.
18. Tötting L, Sandberg O, Bernhardsson M, Ernerudh J, Aspenberg P. Different composition of leucocytes in cortical and cancellous bone healing in a mouse model. *Bone Joint Res.* 2018;7(12):620–628.
19. Hanberg P, Lund A, Søballe K, Bue M. Single-Dose pharmacokinetics of meropenem in porcine cancellous bone determined by microdialysis. *Bone Joint Res.* 2019;8(7):342–348.
20. Sanghani-Kerai A, Osagie-Clouard L, Blunn G, Coathup M. The influence of age and osteoporosis on bone marrow stem cells from rats. *Bone Joint Res.* 2018;7(4):289–297.
21. Nathan K, Lu LY, Lin T, et al. Precise immunomodulation of the M1 to M2 macrophage transition enhances mesenchymal stem cell osteogenesis and differs by sex. *Bone Joint Res.* 2019;8(10):481–488.
22. Muschler GF, Nitto H, Boehm CA, Easley KA. Age- and gender-related changes in the cellularity of human bone marrow and the prevalence of osteoblastic progenitors. *J Orthop Res.* 2001;19(1):117–125.
23. McCann RM, Marsh DR, Horner A, Clarke SA. Body mass index is more predictive of progenitor number in bone marrow stromal cell population than age in men: expanding the predictors of the progenitor compartment. *Tissue Eng Part A.* 2010;16(3):889–896.
24. Levy O, Kuai R, Siren EMJ, et al. Shattering barriers toward clinically meaningful MSC therapies. *Sci Adv.* 2020;6(30):eaba6884.

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