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EDITORIAL

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[1] 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.[2–4] 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.[5]

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?'[6] - 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.[7] 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.[8]

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.[9] This issue is overtly of key importance in conditions known to behave differently in different sexes, such as osteoporosis,[10,11] but may also be important in less obvious conditions such as fracture repair.[12] Therefore, sex should be considered across the whole spectrum of musculoskeletal research, whether it is in cell culture

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studies[13,14] or bioengineering studies such as Koh et al.[15] For in vivo studies, the Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines[16] require that the sex of the animal is clearly stated and many studies now do this (for instance recent studies by Morcos et al,[17] Tätting et al,[18] and Hanberg et al[19] 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.[20–23] 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[24] 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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