

# Do e-cigarettes and vaping have a lower risk of osteoporosis, nonunion, and infection than tobacco smoking?

Nicholson, Thomas; Scott, Aaron; Newton Ede, Matthew; Jones, Simon

DOI:

[10.1302/2046-3758.103.BJR-2020-0327.R1](https://doi.org/10.1302/2046-3758.103.BJR-2020-0327.R1)

License:

Creative Commons: Attribution-NonCommercial-NoDerivs (CC BY-NC-ND)

*Document Version*

Publisher's PDF, also known as Version of record

*Citation for published version (Harvard):*

Nicholson, T, Scott, A, Newton Ede, M & Jones, S 2021, 'Do e-cigarettes and vaping have a lower risk of osteoporosis, nonunion, and infection than tobacco smoking?', *Bone and Joint Journal*, vol. 10, no. 3, pp. 188–191. <https://doi.org/10.1302/2046-3758.103.BJR-2020-0327.R1>

[Link to publication on Research at Birmingham portal](#)

## General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

## Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact [UBIRA@lists.bham.ac.uk](mailto:UBIRA@lists.bham.ac.uk) providing details and we will remove access to the work immediately and investigate.



## ■ BONE BIOLOGY

# Do E-cigarettes and vaping have a lower risk of osteoporosis, nonunion, and infection than tobacco smoking?

**T. Nicholson,  
A. Scott,  
M. Newton Ede,  
S. W. Jones**

*From Institute of  
Inflammation and  
Ageing, University  
of Birmingham,  
Birmingham, UK*

**Cite this article:** *Bone Joint Res* 2021;10(3):188–191.

**Keywords:** Vaping, E-Cigarette, Osteoblast, Bone

Cigarette smoking is significantly associated with reduced bone mineral density (BMD), increased risk of fracture, and reduced fracture healing.<sup>1,2</sup> Smoking is also independently associated with increased incidence of post-surgery complications such as infection and aseptic loosening following arthroplasty.<sup>3–6</sup> While cigarette consumption has declined over the past decade, the use of electronic cigarettes (E-cigarettes), or vaping, has risen dramatically, partly due to being regarded as a safer alternative to smoking.<sup>7–9</sup> Indeed, Public Health England guidance suggests that E-cigarettes are 95% safer than cigarettes, fuelling public perception of negligible risk.<sup>8</sup> Increased use of E-cigarettes will undoubtedly represent a harm reduction in comparison to cigarettes due to less exposure to carcinogens and toxicants.<sup>2,10</sup> However, E-cigarette usage still results in systemic exposure to numerous and potentially harmful vapour constituents, including nicotine (in nicotine-containing liquids), flavouring chemicals, and reactive aldehydes, particularly for highly vascularized tissues such as the bone.<sup>2</sup> Critically, recent data suggest that vaping may be considerably more harmful than first thought.<sup>11</sup> Despite this, there has been limited investigation into the impact of E-cigarette usage on bone health, particularly over extended time periods. Here we draw together data from studies that have investigated the impact of E-cigarette vapour and its major constituents on bone, highlighting the mechanistic and functional results.

E-cigarette vapour has been reported to have a substantial impact on bone architecture in vivo, with microfractures evident in the femurs of mice following six months of chronic exposure, even following exposure to aerosols free of flavourings and nicotine.<sup>12</sup> However, no effect on cortical bone

strength, bone stiffness, or hydroxyapatite content was observed in this study.<sup>12</sup> In addition, nicotine-rich E-cigarette vapour has been demonstrated to induce apoptosis and cause a reduction in both mineralization and alkaline phosphatase activity of Saos-2 osteoblasts (a human osteoblast-like cell line, the main cell type responsible for bone formation).<sup>13</sup> Commercially available E-liquids also reduced cellular viability of Saos-2 and MG-63 cells (another osteoblast-like cell line), independent of the presence of nicotine.<sup>14</sup> Although application of E-cigarette liquid does not directly mimic usage, as the chemical composition of E-cigarettes can change upon vaping,<sup>15–18</sup> such data highlight potential harm to bone health. Furthermore, the differentiation of bone marrow-derived mesenchymal stem cells (MSCs) towards the osteoblast lineage plays an important role in the regulation of bone turnover, particularly post injury. In response to treatment with E-cigarette smoke extract, MSCs cultured in osteogenic conditions displayed reduced expression of osteoblast genes, including alkaline phosphatase and type 1 collagen messenger RNA (mRNA) expression, and decreased mineralization, potentially mediated by loss of connexin43.<sup>19</sup>

There is evidence that E-cigarette users self-titrate consumption to achieve a nicotine dose similar to that obtained from cigarettes.<sup>20</sup> Therefore, the impact of nicotine on bone following the use of nicotine-containing E-cigarettes may be comparable to that of conventional cigarettes. Critically, the expression of nicotinic acetylcholine receptor subunits has been reported in both human bone tissue and primary human osteoblasts, with expression upregulated in response to nicotine.<sup>21,22</sup> Nicotine appears to have a bimodal effect on proliferation of primary human osteoblasts, with low doses

Correspondence should be sent to  
Simon W. Jones; email:  
s.w.jones@bham.ac.uk

doi: 10.1302/2046-3758.103.BJR-  
2020-0327.R1

*Bone Joint Res* 2021;10(3):188–  
191.

increasing proliferation and higher doses ( $> 0.1 \mu\text{M}$ ) significantly reducing proliferation and inducing apoptosis.<sup>21,23</sup> Functionally, there is evidence that nicotine reduces human primary osteoblast alkaline phosphatase activity and osteogenic gene expression, including runt-related transcription factor 2 (RUNX2) and osteonectin.<sup>24</sup> Furthermore, nicotine has also been demonstrated to increase matrix metalloproteinases-1, 2, 3, and 13 mRNA expression in Saos-2 cells, and drive mitochondrial stress in murine osteoblast-like cells, resulting in increased reactive oxygen species production.<sup>22,25,26</sup>

In contrast to osteoblasts, osteoclasts are primarily responsible for bone resorption. Therefore a positive balance between osteoclast and osteoblast activity leads to a reduction in bone mass. Osteoclasts also express  $\alpha 1$  to 5, 7, 9, and 10 nicotine receptor subtypes, with  $\alpha 7$  mRNA increasing in response to nicotine treatment.<sup>27</sup> In vitro data examining the role of nicotine on osteoclast function are conflicting. On the one hand, nicotine increased RAW264.7 osteoclast carbonic anhydrase expression, promoting demineralization.<sup>27</sup> However, there is also evidence that nicotine reduces bone resorption by decreasing V-ATPase expression and the planar area of the resorption.<sup>27</sup> Contrasting results have also been observed in vivo. Firstly, knockout of  $\alpha 7$  nicotine receptors in mice resulted in decreased osteoclastogenesis and increased bone mass.<sup>28,29</sup> However, nicotine-mediated activation of  $\alpha 7$  receptors in mice has been demonstrated to upregulate receptor activator of nuclear factor kappa-B ligand (RANKL) expression, promoting osteoclast activation and bone resorption.<sup>29</sup>

The most common carrier agents/humectants used in E-cigarette liquids include propylene glycol and vegetable glycerine. E-cigarette use results in thermal degradation of such humectants, generating carbonyl compounds such as formaldehyde, acetaldehyde, and acrolein.<sup>15,30</sup> Importantly, increased amounts of aldehyde compounds were detected in exhaled breath after vaping, while exhaled formaldehyde concentrations were similar to traditional cigarettes ( $\sim 5 \mu\text{g-puff}^{-1}$ ).<sup>31</sup> Although the effect of E-cigarette-derived carbonyl compounds on bone cell function has not been studied directly, there is evidence that aldehydes can reduce proliferation and increase cell death of U2OS cells (human osteoblastic cell line) in a dose-dependent manner,<sup>32,33</sup> and reduce osteoblast alkaline phosphatase activity and mineralization.<sup>34</sup> Acetaldehyde has also been shown to stimulate peroxisome proliferator-activated receptor (PPAR $\gamma$ ) expression in murine osteoblasts, inhibiting osteoblast differentiation.<sup>35</sup> Additionally, genetic polymorphisms resulting in reduced aldehyde dehydrogenase, mitochondrial (ALDH2) cause a build-up of acetaldehyde in humans, lower BMD, and a significantly increased rate of hip fracture and osteoporosis.<sup>36,37</sup>

The wide variety of E-cigarette flavouring liquids available for consumption (over 8,000 to date) is a primary contributing factor to the rise in popularity of

E-cigarette usage, especially among younger individuals and those who previously did not smoke cigarettes.<sup>38-40</sup> However, there is limited regulation and quality control of flavouring compounds present in E-cigarette liquids. Flavouring chemicals have been demonstrated to have harmful effects on other cell types such as immune cells,<sup>11</sup> and atomization of flavouring chemicals including linalool, dipentene, and citral causes free radical production.<sup>41-43</sup> Despite this, there is a dearth of studies investigating physiological effects of flavouring chemicals on bone directly.

Traditional cigarettes are associated with the inhalation of metal particulates, including chromium, cadmium, lead, and nickel, all of which are known to have a variety of harmful effects.<sup>44-46</sup> Emerging data have demonstrated that metal particulates and nanoparticles are also generated from E-cigarettes, with concentrations in many cases similar or exceeding those from cigarette smoke.<sup>47,48</sup> However, the effect of E-cigarette-derived metal particulates on bone has not yet been reported.

The development of E-cigarette devices has also resulted in their use to vape cannabidiol (CBD), the major non-psychoactive constituent of cannabis, due to its purported analgesic, anti-inflammatory, and anti-epileptic properties.<sup>49-51</sup> Again, although no direct study of the effect of vaping CBD on bone has been performed, data surrounding direct administration of CBD suggest a largely positive impact on bone, including reduced bone loss following the induction of periodontal disease,<sup>52</sup> promotion of fracture healing,<sup>53</sup> and recovery following injury in rats.<sup>54,55</sup> There is also evidence that CBD can suppress osteoclastogenesis and reduce the function of human osteoclasts.<sup>56,57</sup>

To date there has been little investigation into the effect of E-cigarette vapour on bone and bone cell function. Current data suggest that exposure of both osteoblasts and osteoclasts to high concentrations of nicotine may reduce their viability and impair function. Similarly, aldehydes and flavouring chemicals may also negatively impact osteoblast viability and ability to form bone. However, such findings are predominantly derived from studies using bone cell lines, with limited use of human osteoblasts or osteoclasts. Understanding how E-cigarette vapour components may mediate human bone cell function, in addition to long-term studies to determine the potential harm of chronic E-cigarette use on human bone, will be important to inform users and healthcare providers of potential risks, particularly regarding bone healing following orthopaedic surgery and injury.

## Twitter

Follow S. W. Jones @UoB\_JonesLab

## References

1. Patel RA, Wilson RF, Patel PA, Palmer RM. The effect of smoking on bone healing: a systematic review. *Bone Joint Res.* 2013;2(6):102–111.
2. Hernigou J, Schuind F. Tobacco and bone fractures: a review of the facts and issues that every orthopaedic surgeon should know. *Bone Joint Res.* 2019;8(6):255–265.

3. Singh JA, Schleck C, Harmsen WS, Jacob AK, Warner DO, Lewallen DG. Current tobacco use is associated with higher rates of implant revision and deep infection after total hip or knee arthroplasty: a prospective cohort study. *BMC Med*. 2015;13:283.
4. Matharu GS, Mouchti S, Twigg S, et al. The effect of smoking on outcomes following primary total hip and knee arthroplasty: a population-based cohort study of 117,024 patients. *Acta Orthop*. 2019;90(6):559–567.
5. Teng S, Yi C, Krettek C, Jagodzinski M. Smoking and risk of prosthesis-related complications after total hip arthroplasty: a meta-analysis of cohort studies. *PLoS One*. 2015;10(4):e0125294.
6. Abrahamson B, Brask-Lindemann D, Rubin KH, Schwarz P. A review of lifestyle, smoking and other modifiable risk factors for osteoporotic fractures. *Bonekey Rep*. 2014;3:574.
7. Rom O, Pecorelli A, Valacchi G, Reznick AZ. Are e-cigarettes a safe and good alternative to cigarette smoking? *Ann N Y Acad Sci*. 2015;1340:65–74.
8. McNeill A, Brose L S, Calder R, Bauld L, Robson D. Evidence review of e-cigarettes and heated tobacco products 2018 a report commissioned by Public Health England. *Public Health England*. 2018.
9. Cornish D, Brookman A, Horton M, Scanlon S. Adult smoking habits in the UK: 2018. 2019. Office for National Statistics. <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandlifeexpectancies/bulletins/adultsmokinghabitsingreatbritain/2018> (date last accessed 22 February 2021).
10. Goniewicz ML, Knysak J, Gawron M, et al. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tob Control*. 2014;23(2):133–139.
11. Scott A, Lugg ST, Aldridge K, et al. Pro-inflammatory effects of e-cigarette vapour condensate on human alveolar macrophages. *Thorax*. 2018;73(12):1161–1169.
12. Reumann MK, Schaefer J, Titz B, et al. E-vapor aerosols do not compromise bone integrity relative to cigarette smoke after 6-month inhalation in an ApoE<sup>-/-</sup> mouse model. *Arch Toxicol*. 2020;94(6):2163–2177.
13. Rouabhia M, Alanazi H, Park HJ, Goncalves RB, Smoke C. Cigarette smoke and e-cigarette vapor dysregulate osteoblast interaction with titanium dental implant surface. *J Oral Implantol*. 2019;45(1):2–11.
14. Otero CE, Noeker JA, Brown MM, et al. Electronic cigarette liquid exposure induces flavor-dependent osteotoxicity and increases expression of a key bone marker, collagen type I. *J Appl Toxicol*. 2019;39(6):888–898.
15. Uchiyama S, Noguchi M, Sato A, Ishitsuka M, Inaba Y, Kunugita N. Determination of thermal decomposition products generated from e-cigarettes. *Chem Res Toxicol*. 2020;33(2):576–583.
16. Jensen RP, Strongin RM, Peyton DH. Solvent chemistry in the electronic cigarette reaction vessel. *Sci Rep*. 2017;7:42549.
17. Geiss O, Bianchi I, Barrero-Moreno J. Correlation of volatile carbonyl yields emitted by e-cigarettes with the temperature of the heating coil and the perceived sensorial quality of the generated vapours. *Int J Hyg Environ Health*. 2016;219(3):268–277.
18. Uchiyama S, Ohta K, Inaba Y, Kunugita N. Determination of carbonyl compounds generated from the e-cigarette using coupled silica cartridges impregnated with hydroquinone and 2,4-dinitrophenylhydrazine, followed by high-performance liquid chromatography. *Anal Sci*. 2013;29(12):1219–1222.
19. Shaito A, Saliba J, Husari A, et al. Electronic cigarette smoke impairs normal mesenchymal stem cell differentiation. *Sci Rep*. 2017;7(1):14281.
20. Dawkins LE, Kimber CF, Doig M, Feyerabend C, Corcoran O. Self-titration by experienced e-cigarette users: blood nicotine delivery and subjective effects. *Psychopharmacology*. 2016;233(15–16):2933–2941.
21. Walker LM, Preston MR, Magnay JL, Thomas PB, El Haj AJ. Nicotinic regulation of c-fos and osteopontin expression in human-derived osteoblast-like cells and human trabecular bone organ culture. *Bone*. 2001;28(6):603–608.
22. Katono T, Kawato T, Tanabe N, et al. Nicotine treatment induces expression of matrix metalloproteinases in human osteoblastic SaOS-2 cells. *Acta Biochim Biophys Sin*. 2006;38(12):874–882.
23. Marinucci L, Balloni S, Fettucciari K, Bodo M, Tasesa VN, Antognelli C. Nicotine induces apoptosis in human osteoblasts via a novel mechanism driven by H<sub>2</sub>O<sub>2</sub> and entailing Glyoxalase 1-dependent MG-H1 accumulation leading to TG<sub>2</sub>-mediated NF-κB desensitization: Implication for smokers-related osteoporosis. *Free Radic Biol Med*. 2018;117:6–17.
24. Marinucci L, Bodo M, Balloni S, Locci P, Baroni T. Sub-toxic nicotine concentrations affect extracellular matrix and growth factor signaling gene expressions in human osteoblasts. *J Cell Physiol*. 2014;229(12):2038–2048.
25. Chen Y-J, Lee S-S, Huang F-M, Chang Y-C. Effects of nicotine on differentiation, prostaglandin E<sub>2</sub>, and nitric oxide production in cementoblasts. *J Dent Sci*. 2015;10(4):431–436.
26. Li Y, Yu C, Shen G, et al. Sirt3-MnSOD axis represses nicotine-induced mitochondrial oxidative stress and mtDNA damage in osteoblasts. *Acta Biochim Biophys Sin*. 2015;47(4):306–312.
27. Tanaka H, Tanabe N, Kawato T, et al. Nicotine affects bone resorption and suppresses the expression of cathepsin K, MMP-9 and vacuolar-type H(+)-ATPase d2 and actin organization in osteoclasts. *PLoS One*. 2013;8(3):e59402.
28. Mandl P, Hayer S, Karonitsch T, et al. Nicotinic acetylcholine receptors modulate osteoclastogenesis. *Arthritis Res Ther*. 2016;18:63.
29. Mito K, Sato Y, Kobayashi T, et al. The nicotinic acetylcholine receptor α7 subunit is an essential negative regulator of bone mass. *Sci Rep*. 2017;7:45597.
30. Bekki K, Uchiyama S, Ohta K, Inaba Y, Nakagome H, Kunugita N. Carbonyl compounds generated from electronic cigarettes. *Int J Environ Res Public Health*. 2014;11(11):11192–11200.
31. Samburova V, Bhattarai C, Strickland M, et al. Aldehydes in exhaled breath during e-cigarette Vaping: pilot study results. *Toxics*. 2018;6(3):E46:46.
32. Ho Y-C, Huang F-M, Chang Y-C. Cytotoxicity of formaldehyde on human osteoblastic cells is related to intracellular glutathione levels. *J Biomed Mater Res B Appl Biomater*. 2007;83(2):340–344.
33. Giuliani N, Girasole G, Vescovi PP, Passeri G, Pedrazzoni M. Ethanol and acetaldehyde inhibit the formation of early osteoblast progenitors in murine and human bone marrow cultures. *Alcohol Clin Exp Res*. 1999;23(2):381–385.
34. Pereira ML, Carvalho JC, Peres F, Fernandes MH. Simultaneous effects of nicotine, acrolein, and acetaldehyde on osteogenic-induced bone marrow cells cultured on plasma-sprayed titanium implants. *Int J Oral Maxillofac Implants*. 2010;25(1):112–122.
35. Hoshi H, Hao W, Fujita Y, et al. Aldehyde-stress resulting from ALDH2 mutation promotes osteoporosis due to impaired osteoblastogenesis. *J Bone Miner Res*. 2012;27(9):2015–2023.
36. Takeshima K, Nishiwaki Y, Suda Y, et al. A missense single nucleotide polymorphism in the ALDH2 gene, rs671, is associated with hip fracture. *Sci Rep*. 2017;7(1):428.
37. Yamaguchi J, Hasegawa Y, Kawasaki M, et al. Aldh2 polymorphisms and bone mineral density in an elderly Japanese population. *Osteoporos Int*. 2006;17(6):908–913.
38. Zhu SH, Sun JY, Bonnevill E, et al. Four hundred and sixty brands of e-cigarettes and counting: implications for product regulation. *Tob Control*. 2014;23 Suppl 3(Suppl 3):iii3–iii9.
39. Tsai J, Walton K, Coleman BN, et al. Reasons for electronic cigarette use among middle and high school students - national youth tobacco survey, United States, 2016. *MMWR Morb Mortal Wkly Rep*. 2018;67(6):196–200.
40. Harrell MB, Weaver SR, Loukas A, et al. Flavored e-cigarette use: characterizing youth, young adult, and adult users. *Prev Med Rep*. 2017;5:33–40.
41. Bitzer ZT, Goel R, Reilly SM, et al. Effect of flavoring chemicals on free radical formation in electronic cigarette aerosols. *Free Radic Biol Med*. 2018;120:72–79.
42. Goel R, Durand E, Trushin N, et al. Highly reactive free radicals in electronic cigarette aerosols. *Chem Res Toxicol*. 2015;28(9):1675–1677.
43. Domazetovic V, Marcucci G, Iantomasi T, Brandi ML, Vincenzini MT. Oxidative stress in bone remodeling: role of antioxidants. *Clin Cases Miner Bone Metab*. 2017;14(2):209–216.
44. Cheng LC, Lin CJ, Liu HJ, Li L-A. Health risk of metal exposure via inhalation of cigarette sidestream smoke particulate matter. *Environ Sci Pollut Res Int*. 2019;26(11):10835–10845.
45. Behera SN, Xian H, Balasubramanian R. Human health risk associated with exposure to toxic elements in mainstream and sidestream cigarette smoke. *Sci Total Environ*. 2014;472:947–956.
46. Bernhard D, Rossmann A, Wick G. Metals in cigarette smoke. *IUBMB Life*. 2005;57(12):805–809.
47. Palazzolo DL, Crow AP, Nelson JM, Johnson RA. Trace metals derived from electronic cigarette (ECIG) generated aerosol: potential problem of ECIG devices that contain nickel. *Front Physiol*. 2016;7:663.
48. Williams M, Villarreal A, Bozhilov K, Lin S, Talbot P. Metal and silicate particles including nanoparticles are present in electronic cigarette cartomizer fluid and aerosol. *PLoS One*. 2013;8(3):e57987.
49. Nagarkatti P, Pandey R, Rieder SA, Hegde VL, Nagarkatti M. Cannabinoids as novel anti-inflammatory drugs. *Future Med Chem*. 2009;1(7):1333–1349.
50. Russo EB. Cannabinoids in the management of difficult to treat pain. *Ther Clin Risk Manag*. 2008;4(1):245–259.
51. Silvestro S, Mammana S, Cavalli E, Bramanti P, Mazzon E. Use of cannabidiol in the treatment of epilepsy: efficacy and security in clinical trials. *Molecules*. 2019;24(8):E1459:1459.

52. **Napimoga MH, Benatti BB, Lima FO, et al.** Cannabidiol decreases bone resorption by inhibiting RANK/RANKL expression and pro-inflammatory cytokines during experimental periodontitis in rats. *Int Immunopharmacol.* 2009;9(2):216–222.
53. **Kogan NM, Melamed E, Wasserman E, et al.** Cannabidiol, a major non-psychoactive cannabis constituent enhances fracture healing and stimulates lysyl hydroxylase activity in osteoblasts. *J Bone Miner Res.* 2015;30(10):1905–1913.
54. **Silveira JW, Issy AC, Castania VA, et al.** Protective effects of cannabidiol on lesion-induced intervertebral disc degeneration. *PLoS One.* 2014;9(12):e113161.
55. **Li D, Lin Z, Meng Q, Wang K, Wu J, Yan H.** Cannabidiol administration reduces sublesional cancellous bone loss in rats with severe spinal cord injury. *Eur J Pharmacol.* 2017;809:13–19.
56. **Tsuchiya M, Kayamori K, Wada A, et al.** A novel, tumor-induced osteoclastogenesis pathway insensitive to denosumab but interfered by cannabidiol. *Int J Mol Sci.* 2019;20(24):6211.
57. **Whyte LS, Ryberg E, Sims NA, et al.** The putative cannabinoid receptor GPR55 affects osteoclast function in vitro and bone mass in vivo. *Proc Natl Acad Sci U S A.* 2009;106(38):16511–16516.

#### Author information:

- T. Nicholson, BSc, PhD, Post-doctoral Research Associate
- S. W. Jones, BSc, PhD, Reader in Musculoskeletal Ageing MRC-ARUK Centre for Musculoskeletal Ageing Research, Medical School, Queen Elizabeth Hospital, University of Birmingham, Birmingham, UK.
- A. Scott, BSc, PhD, Lecturer, Birmingham Acute Care Research Group Institute of Inflammation and Ageing (IIA), University of Birmingham, Birmingham, UK.
- M. Newton Ede, MBChB, MRCS(Eng), FRCS(Tr&Orth), Consultant Orthopaedic Surgeon, Royal Orthopaedic Hospital, Birmingham, UK.

#### Author contributions:

- T. Nicholson: Wrote the first draft of the manuscript, Reviewed, edited, and approved the final manuscript.
- A. Scott: Conceptualized the study, Reviewed, edited, and approved the manuscript.
- M. Newton Ede: Conceptualized the study, Reviewed and approved the final manuscript.
- S. W. Jones: Conceptualized the study, Reviewed, edited, and approved the manuscript.

#### Funding statement:

- The author or one or more of the authors have received or will receive benefits for personal or professional use from a commercial party related directly or indirectly to the subject of this article. This work was supported by a funding grant from NuVasive Ltd and from MRC-Versus Arthritis Centre for Musculoskeletal Ageing Research (MR/K00414X/1). The funders had no role in the decision to publish, or preparation of the manuscript.

#### ICMJE COI statement:

- S. W. Jones and T. Nicholson report an institutional grant from NuVasive Ltd related to this article. A. Scott and T. Nicholson report an institutional grant from MRC-Versus Arthritis Centre for Musculoskeletal Ageing Research (MR/K00414X/1), also related to this article.

#### Acknowledgements:

- The authors acknowledge support from the funders NuVasive Ltd and the MRC-Versus Arthritis Centre for Musculoskeletal Ageing Research.

© 2021 Author(s) et al. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives (CC BY-NC-ND4.0) licence, which permits the copying and redistribution of the work only, and provided the original author and source are credited. See <https://creativecommons.org/licenses/by-nc-nd/4.0/>.