Osteoporosis International (2019) 30:1709–1710
https://doi.org/10.1007/s00198-019-05013-7

LETTER TO THE EDITOR

# Glucagon-like peptide-1 receptor agonists and fracture risk—limitations to current knowledge

K. Hygum[1] · T. Harsløf[1] · B. Langdahl[1] · J. Starup-Linde[1,2]

Received: 29 August 2018 / Accepted: 16 September 2018 / Published online: 22 May 2019


We welcome the meta-analysis by Zhang and colleagues that report that glucagon-like peptide-1 receptor agonists (GLP-1 RAs) were associated with a decreased fracture risk compared to users of placebo or other anti-hyperglycemic drugs [1]. We acknowledge the immense work-load of the authors in collating evidence from 54 randomized controlled trials, but we would like to point out that the findings may be limited by several factors. First, the duration of the included trials is limited as most studies have a follow-up of 52 weeks or less and only one study reports a follow-up of 260 weeks [1]. For studies with a short follow-up period, a potential decrease in fracture risk is likely caused by a reduction in falls by reducing hypoglycemic events rather than improvement of bone mechanical competences. Second, the study reports 137 fractures in users of GLP-1 RAs. However, supplemental Fig. 3 shows that only 4 vertebral fractures and 16 hip fractures were recorded [1]. We would like to emphasize that many other minor fractures are most likely related to falls and other trauma. Third, the authors perform sensitivity analysis and state that the results were mostly similar to the results of the main analysis. However, when inspecting supplemental Table 4, it is evident that all results turned non-significant in sensitivity analysis. Fourth, the study compares GLP-1 RAs to placebo and other anti-hyperglycemic drugs, nonetheless no results are presented in neither paper nor supplemental material on GLP-1 RAs compared with other anti-hyperglycemic drugs. Despite this, the authors conclude in the final paragraph of the paper that GLP-1 RAs were associated with a decreased fracture risk compared to users of placebo or other anti-hyperglycemic drugs. The meta-analysis only reports a significantly decreased risk of fracture when comparing exenatide treatment with placebo. Three studies reported on exenatide compared to placebo, with follow-up between 28 and 56 weeks and as stated above, we propose that a potential risk reduction would be due to a reduction in falls [1]. In epidemiological studies, GLP-1 RAs have shown neutral effects on fracture risk when compared to the use of other anti-hyperglycemic drugs [2, 3]. However, the comparator in these studies includes combination of different drugs as well as metformin monotherapy thus there is also a demand for comparable reference groups [2]. Also, the epidemiological evidence is limited by short-treatment period of maximum 1.7 years [3]. One previous meta-analysis of randomized controlled trials showed neutral effects [4] on fracture risk, and another meta-analysis found an increased risk of fracture in users of exenatide but a decreased risk in liraglutide [5]. Taken together, the current evidence on the use of GLP-1 RAs and fracture risk is limited by studies that did not have fracture or changes in bone metabolism as primary endpoints, a lack of relevant fractures and a short follow-up period. Currently, the evidence suggests neutral effects of GLP-1 RAs on fracture risk, and also that a possible beneficial effect is most likely due to fall reduction caused by a reduction in hypoglycemic events.

✉ J. Starup-Linde
jakolind@rm.dk

[1] Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Palle Juul Jensens Boulevard 99, DK-8200 Aarhus N, Denmark

[2] Steno Diabetes Center North Jutland, Aalborg University Hospital, Mølleparkvej 4, 9000 Aalborg, Denmark

## Compliance with ethical standards

**Conflict of interest** BL reports research grants (institution) from Amgen and Novo Nordisk. BL serves on advisory boards for Amgen, Eli Lilly, and UCB and has received honoraria for lecturing from Amgen, Eli Lilly, UCB, and TEVA.

TH has received lecture fees from Eli Lilly, Amgen, and AstraZeneca. JS-L reports personal fees from Gilead Sciences Denmark and personal fees from Eli Lilly Denmark, outside the submitted work.

## References

1. Zhang YS, Weng WY, Xie BC, Meng Y, Hao YH, Liang YM, Zhou ZK (2018) Glucagon-like peptide-1 receptor agonists and fracture risk: a network meta-analysis of randomized clinical trials. Osteoporos Int 29:2639–2644. https://doi.org/10.1007/s00198-018-4649-8
2. Driessen JH, van Onzenoort HA, Starup-Linde J, Henry R, Burden AM, Neef C, van den Bergh JP, Vestergaard P, de Vries F (2015) Use of glucagon-like-peptide 1 receptor agonists and risk of fracture as compared to use of other anti-hyperglycemic drugs. Calcif Tissue Int. https://doi.org/10.1007/s00223-015-0037-y
3. Driessen JH, de Vries F, van Onzenoort H, Harvey NC, Neef C, van den Bergh J, Vestergaard P, Henry RM (2016) The use of incretins and fractures - a meta-analysis on population-based real life data. Br J Clin Pharmacol 83:923–926. https://doi.org/10.1111/bcp.13167
4. Mabilleau G, Mieczkowska A, Chappard D (2014) Use of glucagon-like peptide-1 receptor agonists and bone fractures: a meta-analysis of randomized clinical trials. J Diabetes 6:260–266. https://doi.org/10.1111/1753-0407.12102
5. Su B, Sheng H, Zhang M, Bu L, Yang P, Li L, Li F, Sheng C, Han Y, Qu S, Wang J (2014) Risk of bone fractures associated with glucagon-like peptide-1 receptor agonists' treatment: a meta-analysis of randomized controlled trials. Endocrine 48:107–115. https://doi.org/10.1007/s12020-014-0361-4