Dipeptidyl Peptidase-4 Inhibitors and Bone Fractures

A meta-analysis of randomized clinical trials

MATTEO MONAMI, MD, PHD[1]
ILARIA DICEMBRINI, MD[2]
ALESSANDRO ANTENORE, MD[1]
EDOARDO MANNUCCI, MD[3]

OBJECTIVE—Thiazolidinediones and insulin are associated with a higher risk of fractures in type 2 diabetic patients. Incretin hormones increase bone density in experimental models, but the effect of dipeptidyl peptidase-4 (DPP-4) inhibitors on bone fractures has not been reported so far.

RESEARCH DESIGN AND METHODS—A meta-analysis was performed including all randomized clinical trials with a duration of at least 24 weeks, enrolling patients with type 2 diabetes, comparing DPP-4 inhibitors with placebo or active drugs.

RESULTS—Twenty-eight trials enrolling 11,880 and 9,175 patients for DPP-4 inhibitors and comparators, respectively, were included, reporting 63 fractures. DPP-4 inhibitors, compared with placebo or other treatments, were associated with a reduced risk of fractures (Mantel–Haenszel odds ratio [MH-OR] 0.60, 95% CI 0.37–0.99, $P = 0.045$), even after the exclusion of comparisons with thiazolidinediones or sulfonylureas (MH-OR 0.56, 0.33–0.93, $P = 0.026$).

CONCLUSIONS—The present meta-analysis suggests that treatment with DPP-4 inhibitors could be associated with a reduced risk of bone fractures.

Diabetes Care 34:2474–2476, 2011

Type 2 diabetes is associated with an increased risk for bone fractures (1–3). The higher risk could be determined by several factors, including falls, diabetes complications, and comorbidities (2). Moreover, glucose-lowering agents such as thiazolidinediones have been reported to reduce bone density (4,5) and to increase the incidence of fractures in longer-term trials (6,7) and in epidemiologic studies (8). Insulin therapy is also associated with an increased fracture risk (9–11) despite its neutral effect on bone density (12). The increased risk of falls, due to hypoglycemia, could lead to higher fracture risk (10).

Glucagon-like peptide-1 (GLP-1) has been reported to induce osteoblast differentiation (13) and inhibit osteoclastic activity (14); GLP-1 receptor agonists stimulate bone formation in rodents (15). Experimental data in animal models suggest that gastric intestinal polypeptide is also capable of increasing bone density (16,17). Drugs capable of increasing incretin levels, such as dipeptidyl peptidase-4 (DPP-4) inhibitors, could therefore exert beneficial effects on the bone.

RESEARCH DESIGN AND METHODS

A MEDLINE and Embase search for "vildagliptin," "sitagliptin," "saxagliptin," "alogliptin," "linagliptin," and "dutogliptin" was performed for randomized trials up to April 1, 2011. The selection of studies and the subsequent data extraction were performed independently by two of the authors (I.D. and M.M.), and conflicts were resolved by the third investigator (E.M.). Completed but still unpublished trials were identified through a search of www.clinicaltrials.gov website. Food and Drug Administration (www.fda.gov) and European Medicines Agency (www.ema.europa.eu) reviews of approved drugs were also searched for retrieval of unpublished trials.

A meta-analysis was performed including all trials with a duration of ≥24 weeks, enrolling patients with type 2 diabetes, comparing DPP-4 inhibitors with placebo or other active drugs.

Results of unpublished trials were retrieved on www.clinicaltrials.gov, www.clinicalstudyresults.org, and Food and Drug Administration and European Medicines Agency websites.

The quality of trials was assessed using some of the parameters proposed by Jadad et al. (18), used only for descriptive purposes.

The principal outcome was the effect of DPP-4 inhibitors on the incidence of bone fractures reported as serious adverse events. Predefined separate analyses were performed for trials with different DPP-4 inhibitors.

Heterogeneity was assessed by using I^2 statistics. We report the results of the random-effects models because the validity of tests of heterogeneity can be limited with a small number of component studies. To estimate possible publication/disclosure bias, we used funnel plots (Supplementary Fig. A1) and the Begg adjusted rank correlation test (19,20), including published and unpublished, but disclosed, trials. However, because these tests have low statistical power when the number of trials is small (21), undetected bias may still be present. Mantel–Haenszel odds ratio (MH-OR) with 95% CI was calculated for all the adverse events defined above on an intention-to-treat basis, excluding trials with zero events. As a sensitivity analysis, MH-OR in all trials was also calculated with continuity correction.

The meta-analysis was reported following the PRISMA checklist (22) (Supplementary Table 1). All analyses were performed using Comprehensive Meta-analysis Version 2 (Biostat, Englewood, NJ) and SPSS 16.0 (SPSS Inc., Chicago, IL).

From the [1]Section of Geriatric Cardiology and Medicine, Department of Cardiovascular Medicine, Careggi Teaching Hospital, Florence, Italy; the [2]Obesity Agency, Careggi Teaching Hospital, Florence, Italy; and the [3]Diabetes Agency, Careggi Teaching Hospital, Florence, Italy.
Corresponding authors: Edoardo Mannucci, edoardo.mannucci@unifi.it, and Matteo Monami, mmonami@libero.it.
Received 11 June 2011 and accepted 24 August 2011.
DOI: 10.2337/dc11-1099
This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc11-1099/-/DC1.

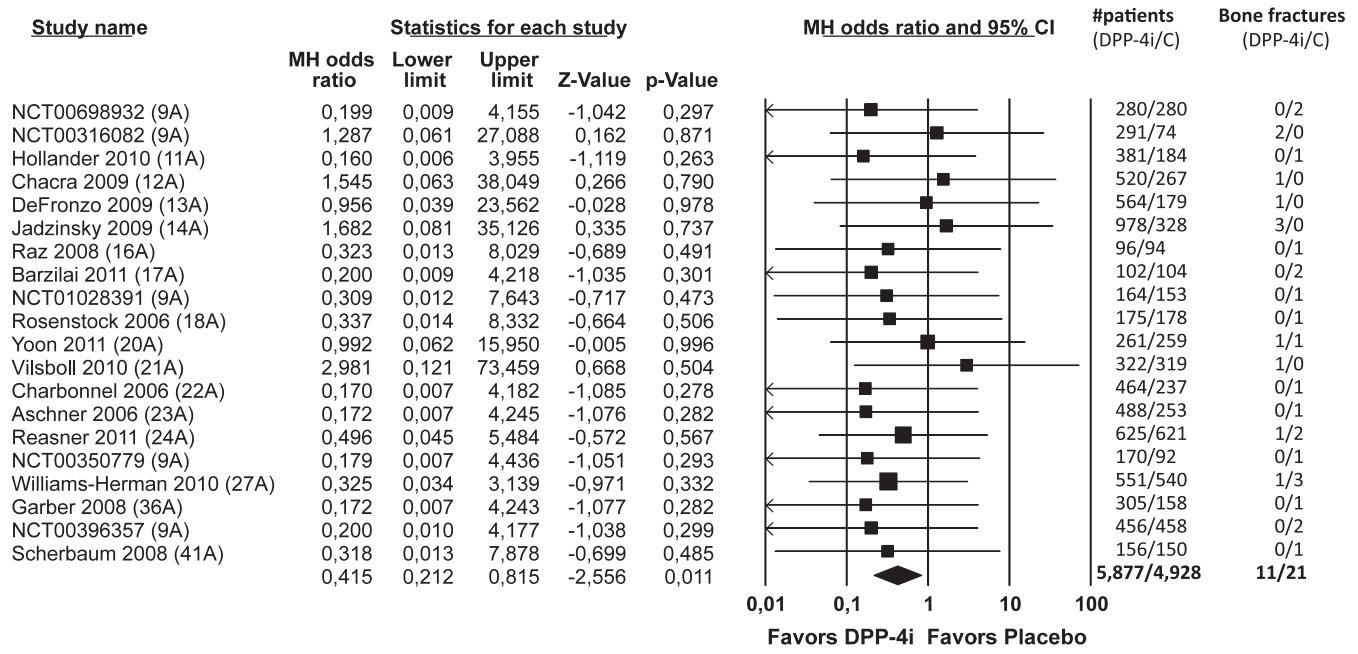

Figure 1—*Subgroup analyses of MH-OR (95% CI) for bone fractures in placebo-controlled trials. DPP-4i, DPP-4 inhibitors.*

This research was performed independently of any funding, as part of the institutional activity of the investigators.

RESULTS—The trial flow is summarized in Supplementary Figure A2. Of 54 available trials, 16 did not disclose bone fractures and 10 reported zero events. The meta-analysis was performed on 28 trials (11,880 and 9,175 patients for DPP-4 inhibitors and comparators, respectively; mean duration of treatment for both was 35 weeks). Of 28 trials, 20 and 7 were placebo- and active comparator-controlled, respectively, whereas one trial included both placebo and active comparator arms (Supplementary Tables 2 and 3). Of 12 unpublished trials, 5, with a planned enrollment of 4,377 patients, were undisclosed and therefore excluded from the analysis. Age, sex, BMI, duration of diabetes, and baseline HbA_{1c} were similar in DPP-4 inhibitor and comparator groups (data not shown).

The Begg adjusted rank correlation test (Kendall τ −0.19; $P = 0.16$) suggested no major publication bias. I^2 test for heterogeneity suggested the use of a random-effects model.

The total number of bone fractures was 63 (26 and 37 with DPP-4 inhibitors and comparators, respectively). The MH-OR for DPP-4 inhibitors was 0.60 (95% CI 0.37–0.99, $P = 0.045$) (Supplementary Fig. A3); the corresponding figure with continuity correction was 0.60 (0.39–0.92, $P = 0.019$). The MH-OR for DPP-4 inhibitors was 0.54 (0.28–1.03, $P = 0.063$) and 0.70 (0.32–1.52, $P = 0.37$) in trials with a duration <52 weeks or ≥52 weeks, respectively; only 7 trials with events and duration ≥52 weeks were available. Similar results (MH-OR 0.41, 0.21–0.81, $P = 0.01$) were obtained in placebo-controlled trials, with no difference across individual DPP-4 inhibitors (Fig. 1).

CONCLUSIONS—Bone fractures are not among the usual end points considered for choosing glucose-lowering therapies. However, therapeutic decisions can modulate the risk of bone fractures (4–9). The results of this meta-analysis should be considered with caution. The duration of the trials included is rather short, not allowing inferences on longer-term effects because of the small number of trials with longer duration. Furthermore, bone fractures were not the principal end points in any of the studies and were reported only as adverse events. This analysis is limited to cases classified as serious adverse events, which are only a fraction of all fractures. Nonserious adverse events were not considered because they are often not reported in detail. Furthermore, it was not possible to discriminate between sexes and between pre- and postmenopausal women; the small number of fractures also prevented separate analyses for different fracture sites. Finally, a reporting bias in favor of DPP-4 inhibitors cannot be entirely ruled out.

Despite those limitations, available trials suggest that DPP-4 inhibitors could have a protective effect on the bone, even after the exclusion of comparisons with drugs associated with a reduction in bone density (thiazolidinediones) or an increase in hypoglycemic risk (sulfonylureas). This action could be due to the increase in circulating levels of GLP-1 and gastric intestinal polypeptide, which are both involved in the regulation of bone metabolism (13–17), whereas it is unlikely that such effect, which has never been reported with other drugs, could be due to the glucose-lowering action of DPP-4 inhibitors.

In view of the results of this meta-analysis, a more careful assessment of bone fractures in trials investigating cardiovascular outcomes with DPP-4 inhibitors is suggested.

Acknowledgments—M.M. has received speaking fees from Bristol-Myers Squibb, Merck, and Takeda. E.M. has received consultancy fees from Merck and Novartis; speaking fees from AstraZeneca, Bristol-Myers Squibb, Merck, and Novartis; and research grants from Merck, Novartis, and Takeda. No other potential conflicts of interest relevant to this article have been reported.

M.M. and E.M. designed the study, collected data, performed analysis, and wrote the manuscript. I.D. and A.A. collected data and performed analysis.

References

1. Vestergaard P. Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes—a meta-analysis. Osteoporos Int 2007;18:427–444
2. Vestergaard P. Bone metabolism in type 2 diabetes and role of thiazolidinediones. Curr Opin Endocrinol Diabetes Obes 2009; 16:125–131
3. Tuominen JT, Impivaara O, Puukka P, Rönnemaa T. Bone mineral density in patients with type 1 and type 2 diabetes. Diabetes Care 1999;22:1196–1200
4. Grey A. Thiazolidinedione-induced skeletal fragility—mechanisms and implications. Diabetes Obes Metab 2009;11: 275–284
5. Yaturu S, Bryant B, Jain SK. Thiazolidinedione treatment decreases bone mineral density in type 2 diabetic men. Diabetes Care 2007;30:1574–1576
6. Kahn SE, Zinman B, Lachin JM, et al.; Diabetes Outcome Progression Trial (ADOPT) Study Group. Rosiglitazone-associated fractures in type 2 diabetes: an analysis from A Diabetes Outcome Progression Trial (ADOPT). Diabetes Care 2008;31:845–851
7. Home PD, Pocock SJ, Beck-Nielsen H, et al.; RECORD Study Team. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet 2009;373:2125–2135
8. Aubert RE, Herrera V, Chen W, Haffner SM, Pendergrass M. Rosiglitazone and pioglitazone increase fracture risk in women and men with type 2 diabetes. Diabetes Obes Metab 2010;12:716–721
9. Monami M, Cresci B, Colombini A, et al. Bone fractures and hypoglycemic treatment in type 2 diabetic patients: a case-control study. Diabetes Care 2008;31: 199–203
10. Schwartz AV, Hillier TA, Sellmeyer DE, et al. Older women with diabetes have a higher risk of falls: a prospective study. Diabetes Care 2002;25:1749–1754
11. Ivers RQ, Cumming RG, Mitchell P, Peduto AJ. Diabetes and risk of fracture: The Blue Mountains Eye Study. Diabetes Care 2001; 24:1198–1203
12. Stolk RP, Van Daele PL, Pols HA, et al. Hyperinsulinemia and bone mineral density in an elderly population: The Rotterdam Study. Bone 1996;18:545–549
13. Sanz C, Vázquez P, Blázquez C, Barrio PA, Alvarez Mdel M, Blázquez E. Signaling and biological effects of glucagon-like peptide 1 on the differentiation of mesenchymal stem cells from human bone marrow. Am J Physiol Endocrinol Metab 2010;298: E634–E643
14. Yamada C, Yamada Y, Tsukiyama K, et al. The murine glucagon-like peptide-1 receptor is essential for control of bone resorption. Endocrinology 2008;149:574–579
15. Nuche-Berenguer B, Moreno P, Portal-Nuñez S, Dapía S, Esbrit P, Villanueva-Peñacarrillo ML. Exendin-4 exerts osteogenic actions in insulin-resistant and type 2 diabetic states. Regul Pept 2010;159:61–66
16. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. Gastroenterology 2007;132:2131–2157
17. Seino Y, Fukushima M, Yabe D. GIP and GLP-1, the two incretin hormones: similarities and differences. J Diabetes Invest 2010;1:8–23
18. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1–12
19. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50: 1088–1101
20. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315:629–634
21. Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. J Clin Epidemiol 2000;53: 1119–1129
22. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264–269, W64