Increased Fracture Risk in Patients Using Insulin Compared to Metformin, Attenuated in Patients Using Combination of Insulin and Metformin: Based on Common Data Models

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Objective: Despite their normal to high bone mineral density, fracture risk was increased in patients with type 2 diabetes. Antidiabetic medications have been suspected to account for the excess risk partly. However, longitudinal comparative studies on the effects of various antidiabetic medications on fractures are limited. We aimed to evaluate the fracture risk of patients using various antidiabetic medications compared to those using metformin.

Methods: We included 6,694 patients aged ≥ 50 years from the common data model (CDM) database between 2008 and 2012, who used the same antidiabetic medications over a year. The patients were grouped as metformin, insulin, sulfonylurea, dipeptidyl-4-inhibitor (DPP4i)+metformin, insulin+metformin, sulfonylurea+insulin, sulfonylurea+metformin, DPP4i+sulfonylurea+insulin, and sulfonylurea+insulin+metformin. The risks of major osteoporotic fractures (MOF) and hip fractures in each group were analyzed using the Cox proportional hazards model compared with the metformin group as a reference.

Results: During a median follow-up duration of 6.1 years, the incidence rates of MOF and hip fracture were 8.36 and 1.53 per 1000 person-year. The mean age was 65.8 years, and 47.7% were women. Compared to metformin users, insulin users showed an increased risk of MOF (hazard ratio [HR] 1.96, 95% confidence interval [CI] 1.28-3.02) and hip fracture (HR 3.06, 95% CI 1.21-7.77) after multivariate adjustments, including age, sex, body mass index (BMI), HbA1c, history of fracture, secondary osteoporosis, rheumatoid arthritis, cardiovascular, cerebrovascular disease, dementia, chronic kidney disease, use of steroid, proton pump inhibitor, and warfarin. Besides, the risk became insignificant in patients using a combination of insulin and metformin in both MOF (HR 1.32, 95% CI 0.77-2.27) and hip fracture risks (HR 2.68, 95% CI 0.56-12.80) after covariates adjustments. In subgroup analysis, insulin users harbored a significantly higher risk for MOF than metformin users only in patients withHbA1c <7%, or BMI <25 kg/m 2.

Conclusion: From real-world data, we found that insulin users were at elevated risk of MOF and hip fracture compared to metformin users, which might be attenuated in users with a combination of insulin and metformin. The increased fracture risk in insulin users was exaggerated in non-obese and well-controlled diabetic patients, indicating the need for routine fracture risk assessment in these patients.

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