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REVIEW ARTICLE

Metformin use and risk of fracture: a systematic review and meta-analysis of observational studies

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Abstract

Introduction No study is available summarizing earlier publications on the association between metformin use and risk of fracture. This systematic review and meta-analysis were conducted to summarize earlier findings on the association between metformin use and risk of fracture.

Methods We conducted a systematic search on all published articles up to October 2018 using online databases including PubMed/Medline, ISI Web of Science, and Scopus. Observational studies that considered metformin use as the exposure variable and bone fracture as the main outcome variable or as one of the outcome variables and participants included were 18 years and older were included in the systematic review. Publications in which hazard ratios (HRs), rate or risk ratios (RRs), or odds ratios (ORs) were reported as effect size were included in the meta-analysis.

Results Totally, three cohort studies, one cross-sectional study, one nested case-control study, and one case-control study were included in this systematic review and meta-analysis. When seven effect sizes from six studies were combined, a significant inverse association between metformin use and risk of fracture was observed (RR 0.82; 95% CI 0.72, 0.93). No significant between-study heterogeneity was found ($I^2 = 22.4\%$, $P_{\text{heterogeneity}} = 0.25$). In addition, no evidence of publication bias was seen using Egger's test ($P = 0.99$).

Conclusion We found that metformin use was inversely associated with the risk of fracture.

Keywords Fracture · Metformin · Meta-analysis · Systematic review

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Abbreviations

AGE	Advanced glycation end products
BMD	Bone mineral density
CI	Confidence interval
F	Female
HR	Hazard ratio
M	Male
NOS	Newcastle-Ottawa Scale
OR	Odds ratio
ROS	Reactive oxygen species
RR	Risk ratio
SE	Standard error

Introduction

Bone disorders, including osteoporosis and fractures, are major health concerns that can impose a huge burden on the individual and healthcare systems [1]. It has been estimated that osteoporosis leads to more than 8.9 million fractures annually in the world [2]. Bone fractures are associated with

increased risk of disability, morbidity, and mortality [3]. Therefore, finding modifiable risk factors of fracture have attracted huge attention.

People with diabetes are at higher risk of bone fractures than those without diabetes [4]. It seems that oral hypoglycemic agents affect bone metabolism [5]. Metformin is the first-line pharmacological therapy in the management of type 2 diabetes [6]. Previous studies have investigated the association between metformin use and risk of fracture; however, results are inconsistent. A case-control study in Denmark reported an inverse association between metformin use and fracture risk [7]. This was also confirmed by a historical cohort study in which treatment with biguanides was protectively associated with risk of fracture [8]. In a cross-sectional study in Japan, metformin use was not associated with risk of fracture [9]. Such findings were also reported by prospective cohort studies [10–12]. However, in a cohort study in Scotland, metformin use was significantly associated with increased risk of hip fracture [13].

To the best of our knowledge, no previous systematic review and meta-analysis have summarized findings from earlier studies on the association between metformin use and risk of fracture. Therefore, we aimed to conduct a comprehensive systematic review and meta-analysis to summarize available data on the association between metformin use and risk of fracture.

Method and materials

Search strategy

We conducted a systematic search on all articles published until October 2018 using online databases including PubMed/Medline, ISI Web of Science, and Scopus using the following keywords: ("Metformin" OR "Glucophage" OR "dimethylbiguanide" OR "dimethylguanylguanidine" OR "metformin HCI") AND ("bone" OR "bone fracture" OR "fracture" OR "osteoporotic fracture" OR "broken bone" OR "bone mineral density" OR "BMD" OR "bone mass density" OR "osteoporosis" OR "bone health"). We did not apply any language or time restrictions in this study. In addition, we did not include unpublished studies and gray literature. Then, a manual search was performed using references from studies already chosen for inclusion to avoid missing any relevant publications. Two reviewers screened the output of the search independently to identify potentially eligible studies.

Inclusion criteria

Each title and abstract was reviewed to identify relevant papers. Full texts of the articles were reviewed if the abstract deemed potentially relevant. Studies with the following criteria were eligible for inclusion: (1) observational studies that considered metformin as the exposure variable and fracture as the main outcome variable or as one of the outcome variables, (2) participants included were 18 years and older, and (3) odds ratios (ORs), rate or risk ratios (RRs), or hazard ratios (HRs) were reported as effect sizes (Table 1).

Exclusion criteria

Letters, commentaries, reviews, and ecological and animal studies were excluded. In our initial search, 905 articles were identified. After elimination of duplicates, 483 papers remained. Finally, 465 studies were excluded on the basis of title and abstract and 18 potentially related articles remained for further assessment. There were eight clinical trials that assessed the effects of metformin use on BMD [14–21]. Since metformin use was compared with other medications, not with placebo in these eight studies, we excluded them from our review. The other four papers were excluded for the following reasons: one had reported the association between combination of biguanides, not just metformin, and risk of fracture [8], one had considered both children and adult population [7], and one had reported no effect size for the association between metformin use and risk of fracture [22]. In another study [23], the authors had reported the risk of fracture in the people with diabetes compared with those without diabetes and no comparison was made for the risk of fracture between patients who were on metformin and those who were not on this medication. Therefore, we excluded that study from our review. After these exclusions, six observational studies [9–13, 24] were considered for inclusion in this systematic review and meta-analysis (Fig. 1).

Data extraction

Two authors (ASM and OS) independently extracted the following data: first author's last name, publication year, study design, country, follow-up duration, participants' mean age or age range, sex, sample size, number of cases, outcome variables, methods used for assessment of fracture, comparison, the maximally adjusted ORs, RRs, or HRs with the corresponding 95% confidence intervals (CIs), and adjustments for potential confounders (Table 1). Any disagreements between the two reviewers were resolved in consultation with the principal investigator (AE).

Quality assessment of studies

The quality of studies included in this systematic review and meta-analysis was evaluated by the Newcastle-Ottawa Scale (NOS) [25]. Based on the NOS method, a maximum of 9 scores can be awarded to each study. In the current analysis, studies with quality scores of > 6 were considered high-quality studies; otherwise, studies were considered to be of low quality.

Table 1 Characteristics of studies examining the association between metformin use and risk of fracture

First author (year)	Design	Country/follow-up duration	Age range/mean age	Sex	Sample size	Cases	Outcome	Outcome assessment	Comparison	OR, RR, or HR (95% CI)	Adjustments
Majumdar et al. (2016)	Prospective	USA/2.2 years	≥ 20	M/F	72,738	741	Osteoporotic fracture	By physician or hospital discharges	Yes vs. no	1.00 (0.80–1.20)	1,2,3,4,5,6,7,8,9,10, 11,12,13,14,15
Napoli et al. (2014)	Prospective	USA/9.1 years	≥ 65	M	779	127	Non-vertebral fracture	Self-reported questionnaire	Yes vs. no	0.96 (0.60–1.54)	1,15,16,17,18,19
Colhoun et al. (2012)	Prospective	Scotland/9 years	65	M/F	173,113	2433	Hip fracture	Record linkage	Yes vs. no	0.75 (0.64–0.87)	1,2,15,20,21,22,23
Puar et al. (2012)	Case-control	Singapore	Cases: 77.3 ± 7.7 Controls: 76.6 ± 6.2	M/F	1116	558	Hip fracture	Hospital discharges	Yes vs. no	0.73 (0.57–0.94)	1,2,16,24,25,26,27
Kanazawa et al. (2010)	Cross-sectional	Japan	60.1 ± 13.2 67.2 ± 9.7	M F	494 344	166 103	Vertebral fracture	X-ray	Yes vs. no	0.57 (0.30–1.09) 0.75 (0.37–1.52)	1,13,24,28,29,30
Monami et al. (2008)	Nested case-control	Italy/4.1 years	Cases: 69.7 ± 11.1 Controls: 68.2 ± 10.5	M/F	332	83	Total fracture	Hospital discharges	Yes vs. no	0.94 (0.54–1.65)	31,32

OR, odds ratio; *RR*, risk ratio; *HR*, hazard ratio; *CI*, confidence interval; *M*, male; *F*, female

1, age; 2, sex; 3, annual income; 4, aggregated diagnosis group comorbidity score; 5, ischemic heart disease; 6, heart failure; 7, dyslipidemia; 8, hypertension; 9, COPD; 10, osteoporosis; 11, rheumatoid arthritis; substance abuse; 12, chronic kidney disease; 13, mean HbA1C; 14, chronic conditions frail; 15, antidiabetic drug use; 16, race/ethnicity; 17, total hip BMD; 18, fell in year before baseline; 19, fasting glucose; 20, years since diagnosis; 21, prior fracture; 22, prior cardiovascular disease; 23, past drug exposure; 24, duration of diabetes; 25, Charlson Comorbidity Index; 26, complications of diabetes mellitus; 27, use of any high-risk medication; 28, BMI; 29, serum creatinine; 30, serum C-peptide; 31, insulin; 32, secretagogues

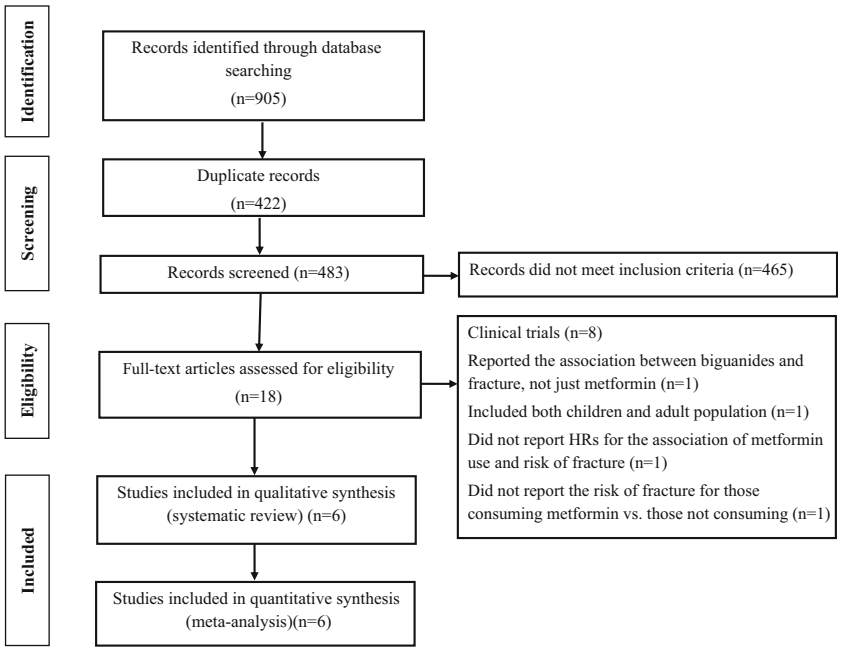

Fig. 1 Flowchart of study selection process

Statistical analysis

All reported ORs, RRs, and HRs and their 95% CIs for the risk of fracture were used to calculate log RRs and their standard errors (SEs). The overall effect size was calculated using the random effects model which incorporate between-study heterogeneity. Between-study heterogeneity was examined using Cochrane's Q test and I-squared. Sensitivity analysis was used to explore the extent to which inferences might depend on a particular study or group of studies. Publication bias was assessed by visual inspection of funnel plots. Formal statistical assessment of funnel plot asymmetry was done using Egger's regression asymmetry test. Statistical analyses were done using Stata MP software, version 14. P values < 0.05 were considered statistically significant.

Results

Study characteristics

Out of 905 retrieved papers, six studies including three cohort studies [10, 11, 13], one cross-sectional study [9], one nested case-control study [12], and one case-control study [24] were included in this systematic review and meta-analysis. Summary of these studies is provided in Table 1. These studies included 248,916 participants aged ≥ 20 years and were published between 2008 and 2016. Two studies were conducted in the USA [10, 11] and one each from Italy [12], Scotland [13], Japan [9], and Singapore [24]. Five studies were performed among both genders [9, 10, 12, 13, 24] and one study was performed on men only [11]. For fracture assessment, the included studies had used different methods including diagnosis by physician [10], self-reported questionnaire [11], X-ray [9], record linkage [13], and hospital discharge information [10, 12, 24]. Included studies had controlled the analyses for age ($n = 5$), sex ($n = 3$), race/ethnicity ($n = 2$), and duration of diabetes ($n = 2$).

Findings from the systematic review

Two cohort studies failed to find any significant association between metformin use and risk of fracture [10, 11]. However, findings from another cohort study revealed a significant inverse association between metformin use and risk of hip fracture [13]. In a cross-sectional study in Japan, the investigators observed no significant association between metformin use and risk of vertebral fracture in either gender [9]. A nested case-control study did not find a significant association between metformin use and risk of bone fractures [12]. In a case-control study in Singapore, a significant inverse association was reported between metformin use and risk of hip fracture [24].

Findings from the meta-analysis

There were three cohort studies [10, 11, 13], one cross-sectional study [9], one nested case-control study [12], and one case-control study [24] that examined the association between metformin use and risk of fracture. The study of Kanazawa et al., that had reported ORs separately for men and women, was considered as two separate studies [9]. Therefore, we had seven effect sizes obtained from six studies in this meta-analysis. When seven effect sizes were combined, a significant inverse association between metformin use and

risk of fracture was found (RR 0.82; 95% CI 0.72, 0.93) (Fig. 2). No significant between-study heterogeneity was seen ($I^2 = 22.4\%$, $P_{\text{heterogeneity}} = 0.25$). In the sensitivity analysis, we found that no particular study influenced the findings significantly. In addition, we found no evidence of publication bias using Egger's test ($P = 0.99$).

Discussion

In this systematic review and meta-analysis, we found a significant inverse association between metformin use and risk of fracture. To the best of our knowledge, this is the first systematic review and meta-analysis that summarize earlier publications on the association between metformin use and risk of fracture.

Individuals with diabetes are at higher risk of fracture and have worse fracture outcomes than individuals without diabetes [26]. Among several factors that might influence the risk of fracture, significant attention has been paid to glucose-lowering medications [5]. Several studies examined the association between metformin use and risk of fracture; however, results are contradictory. As pooling information can provide more precise results than those obtained from individual studies, we conducted a meta-analysis to summarize findings from previous studies on the association between metformin use and risk of fracture. In this systematic review and meta-analysis, we found a significant inverse association between metformin use and risk of fracture. In line with our results, a historical cohort study in the USA showed that treatment with biguanides was protectively associated with risk of fracture [8]. Vestergaard et al. reported that metformin use was associated with a significantly decreased risk of any fractures [7]. However, we did not include that study in our review because both children and adults were recruited into the study. Since the cause of fracture in children might be different from that in adults, we did not consider this publication in the analysis. In addition, Vestergaard et al. had included all types of fractures including fractures from high-energy trauma in their study, which made this study non-comparable to other studies. However, it must be kept in mind that all available studies on the association between metformin use and risk of fracture were of observational design. Limitations originating from observational studies must also be taken into account. In addition, due to limited number of studies on this subject, further studies are required on this topic.

The mechanisms through which metformin might protect against risk of fracture are not well understood yet. It has been shown that metformin stimulates osteoblastic cell differentiation and bone matrix synthesis through the activation of

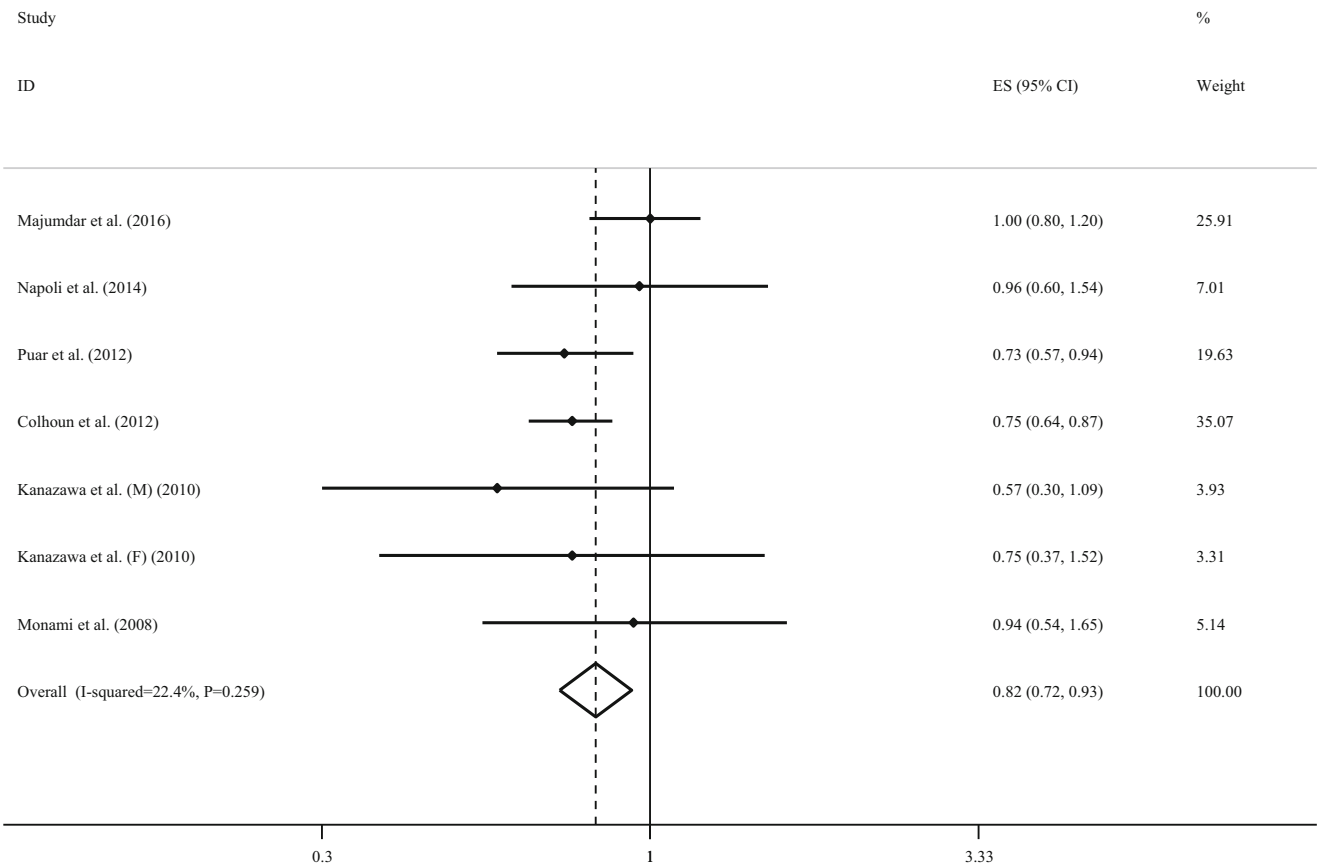

Fig. 2 Forest plot of included studies that examined the association between metformin use and risk of fracture

adenosine 5-monophosphate-activated protein kinase and expression of bone morphogenetic protein-2 [27]. Metformin also prevents advanced glycation end products–induced (AGE) alterations in osteoblastic cells [28] and inhibits formation of reactive oxygen species (ROS) and apoptosis in osteoblasts [29]. Given these findings, it seems that metformin may have a protective effect against risk of fracture.

Being the first systematic review and meta-analysis on the association between metformin use and risk of fracture is the strength of this study. However, some points need to be considered when interpreting our results. Our meta-analysis included a relatively small number of studies. Therefore, these results must be interpreted cautiously. Although all available studies were included, we excluded some studies due to the lack of required data for statistical analysis. Due to the small number of studies, we could not examine the association of metformin use and fracture in different sites and we had to combine fractures from all sites. We also limited our search to published studies only. Although we found no significant evidence of publication bias, lack of considering gray literature might have influenced our findings. In addition, studies included in our systematic review and meta-analysis differed in terms of methods used for assessing bone fractures (self-reported compared with record linkage, X-ray, and by physician and hospital discharge information).

In conclusion, summarizing earlier findings, we observed a significant inverse association between metformin use and risk of fracture. Due to limited information in this regard, further studies are required to reach a definite conclusion.

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Author's contribution ASM and OS contributed to the conception, design, search, statistical analyses, data interpretation, and manuscript drafting. AHK contributed to the manuscript drafting. BL contributed to the design, data interpretation, and manuscript drafting. AE contributed to the conception, design, statistical analyses, data interpretation, and manuscript drafting. AE supervised the study. All authors approved the final manuscript for submission.

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Compliance with ethical standards

Conflicts of interest None.

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