Association between prescribed oral antidiabetic medication for type 2 diabetes mellitus and risk of skin cancer: a systematic review and meta-analysis

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Dear Editor, Skin cancer is most common in light-skinned populations and medications may influence skin cancer susceptibility.[1,2] While oral antidiabetic medication (OADM) can cause skin phototoxicity, some drugs are thought to possess anticarcinogenic properties, based on *in vitro* experiments.[3] Previous studies have provided conflicting information on skin cancer onset after exposure to OADM.[4,5] This study aimed to determine if there was an association between prescribed OADM and the risk of developing skin cancer [basal cell carcinoma (BCC), cutaneous squamous cell carcinoma (cSCC) or melanoma].

The protocol for this systematic review and meta-analysis was registered on PROSPERO (CRD42023416249), and we followed the PRISMA guidelines (https://www.prisma-statement.org/). MEDLINE and Embase were searched on 1 May 2023. Studies had to have included adults prescribed OADM for type 2 diabetes mellitus (T2DM). All genders, geographical locations and ethnicities were included. Exposure was restricted to prescribed OADM for T2DM only; insulin will be explored in a separate study. Eligible comparator groups were either a placebo group, people with T2DM who never used OADM or individuals using a different type of OADM. The outcome assessed was skin cancer, specifically BCC, cSCC and/or melanoma. Studies of individuals with type 1 diabetes were excluded.

Risk of study bias was assessed using the Joanna Briggs Institute tool.[6] Certainty of evidence for outcomes was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool (https://www.gradepro.org/). All processes were conducted by two independent researchers. Random-effects and inverse-variance meta-analyses were conducted. Subgroup analyses were conducted on metformin and rosiglitazone dose and different skin cancer types. Owing to a lack of studies that examined them separately, cSCC and BCC were combined as keratinocyte cancers (KCs).

Our searches found 1173 studies; following title and abstract screening the full texts of 36 articles were retrieved. Overall, 14 studies were included in the systematic review [4 randomized controlled trials (RCTs), 9 cohort studies, 1 case–control study].[4,7–19] Of these, 8 were included in the meta-analyses.[4,7,8,11–13,17,18] Owing to a lack of available literature, RCTs were pooled with observational studies in some analyses. Risk of bias ranged from low to moderate. The overall certainty of evidence for all outcomes was very low, except for the subgroup analysis that examined KCs only, which was low. Adjusted estimates were extracted in preference of crude estimates, where available.

No association was found between OADM and skin cancer risk overall [relative risk (RR) 0.94, 95% confidence interval (CI) 0.74–1.18]. Metformin was associated with a nonsignificantly lower risk of skin cancer compared with nonusers of OADM (RR 0.75, 95% CI 0.49–1.16) and sulfonylurea/tolbutamide (RR 0.71, 95% CI 0.51–1.01). Pioglitazone and rosiglitazone were not associated with a decreased risk of skin cancer vs. nonusers of OADM (RR 1.09, 95% CI 0.80–1.47).

High [> 1500 daily dose units (DDU)] and low doses (< 642 DDU) of metformin (RR 0.73, 95% CI 0.53–1.00) and rosiglitazone (RR 0.89, 95% CI 0.75–1.07) were associated with a reduction in skin cancer risk vs. nonusers of OADM.

The risk of KCs significantly decreased after metformin and rosiglitazone exposure compared with nonusers of OADM (RR 0.77, 95% CI 0.63–0.96). There was no significant association of metformin, pioglitazone and dapagliflozin with melanoma risk vs. nonusers of OADM (RR 0.85, 95% CI 0.35–2.05). This subgroup analysis suggested that OADM may influence KCs more greatly than melanoma. Figure 1 shows the key results of the meta-analysis.

BCC and cSCC have a different origin of malignant cells and developmental pathways than melanoma; thus, it is possible OADM may influence these cells and pathways differently, as demonstrated in a prior meta-analysis, which showed that hydrochlorothiazide affected the risk of cSCC more than melanoma.[20] The dose–response relationship found provides further evidence of causality between OADM and skin cancer risk.

A key strength of this systematic review was that studies of all languages, geographical locations and design were included. However, a limitation was the small number of studies included in some analyses, with uneven weighting, making it unlikely to identify new findings. In addition, polypharmacy was not considered. This review supports prior literature that suggests that OADM possess anticarcinogenic properties and highlights that future research is required to confirm causality between OADM and skin cancer risk.

To summarize, metformin was shown to decrease skin cancer risk vs. sulfonylurea/tolbutamide. Metformin and rosiglitazone exposure was also shown to significantly decrease the risk of BCC and cSCC compared with nonusers of OADM. A dose–response relationship was seen after metformin and rosiglitazone exposure. Based on the GRADE results (very low and low certainty of evidence) there is still a high likelihood that the true effects may be different from those observed in this study.

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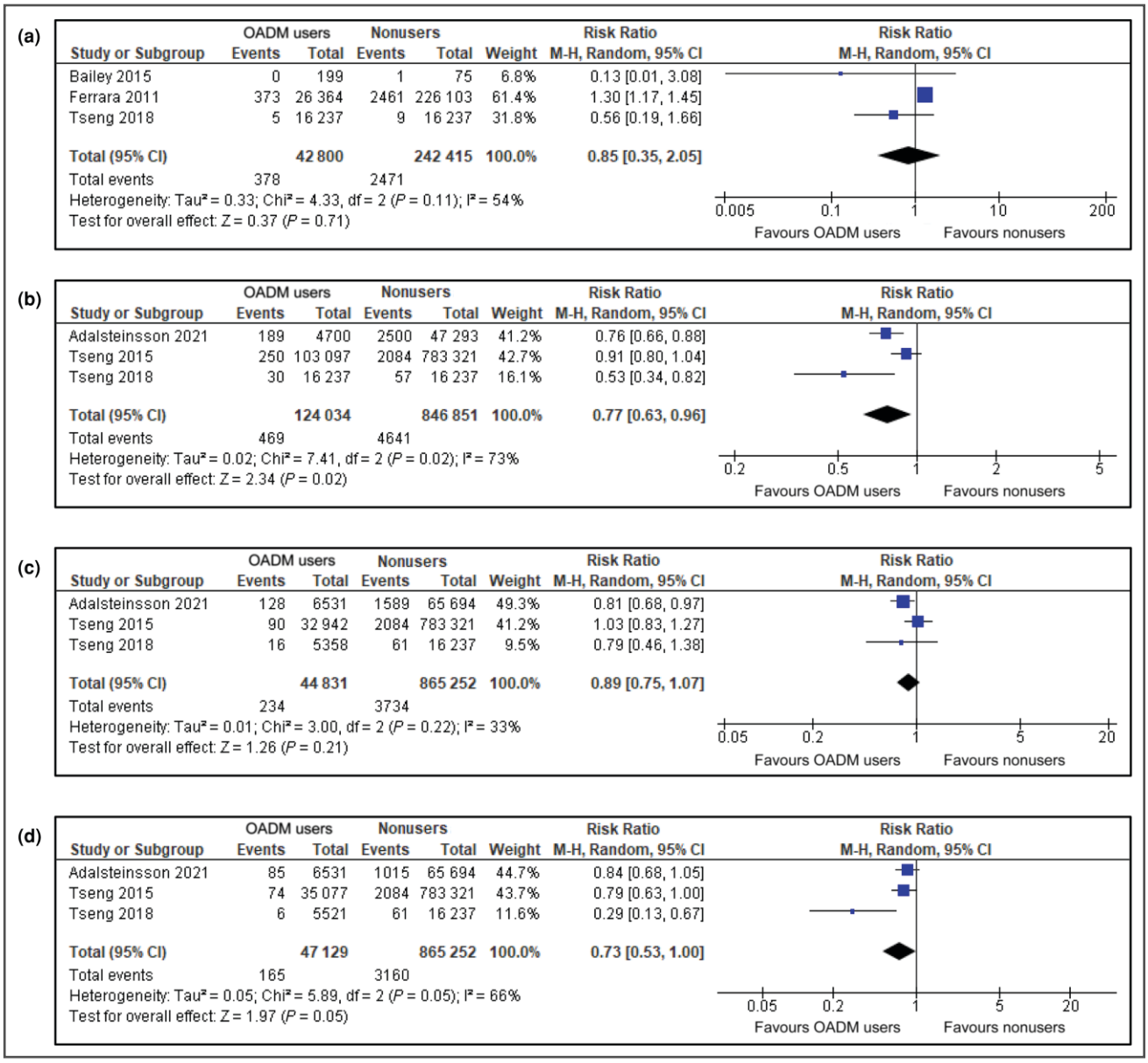

Figure 1 Meta-analyses (random effects) of users of oral antidiabetic medication (OADM) vs. nonusers and the risk of skin cancer. (a) Only studies that reported melanoma were included. (b) Only studies that included basal cell carcinoma and cutaneous squamous cell carcinoma were included. (c) Users of low doses [< 642 daily dose unit (DDU)] of OADM vs. nonusers. (d) Users of high doses (> 1500 DDU) of OADM vs. nonusers; only studies that included OADM doses were included in (c) and (d). CI, confidence interval.

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