COMMENT ON MOORE ET AL.

Increased Risk of Cognitive Impairment in Patients With Diabetes Is Associated With Metformin. Diabetes Care 2013;36:2981–2987

Mark O. Goodarzi

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Moore et al. (1) report that the risk of cognitive impairment is increased in patients with diabetes who take metformin in comparison with patients who do not take metformin. Given that metformin is now recommended as first-line drug treatment for type 2 diabetes (2), such a potentially impactful finding must be based on robust evidence. Unfortunately, several deficiencies call this study's conclusions into question. The authors acknowledged several of these, including lack of data on diabetes duration, diabetes severity, metformin duration, and use of other antidiabetes agents. This does not mitigate against several potential hidden sources of bias, which could render the study's metformin users more susceptible to cognitive impairment for reasons unrelated to metformin. The authors dismiss the potential confounding that metformin users may be more severely affected by hyperglycemia or diabetes complications by stating that this is unlikely because metformin is a first-line therapy. However, this is contradicted by the fact that the majority of patients with diabetes in this study were not taking metformin. Furthermore, metformin's status as a first-line agent is a recent development, particularly in relation to the current study's participants (mean age 73.8 years).

Other factors may serve to render the metformin group ($n = 35$) sicker and thus more prone to cognitive impairment than the group not taking metformin ($n = 91$). We are given no information on what proportion of the nonmetformin group were taking no antidiabetes agents, and therefore were more likely to have milder diabetes than those in the metformin group. Furthermore, 22 patients with impaired glucose tolerance were included in this analysis; most of these subjects (with milder hyperglycemia by definition) were likely incorporated in the nonmetformin group, improving the overall health of that group and potentially decreasing their risk of cognitive impairment. Realizing the impact on sample size, readers would be interested in seeing a version of Table 2 restricted only to those with diabetes. Before recent recommendations that metformin be used as first-line therapy, it was often preferentially prescribed (instead of sulfonylureas, the only other antidiabetes agents available until recently) to patients perceived as having a higher risk of hypoglycemia or a higher risk of harm from hypoglycemia. This might also lead to uneven comorbidity between the metformin and nonmetformin groups.

The authors conclude that B_{12} deficiency may mediate an effect of metformin on cognition, based on the result that adjustment for baseline B_{12} levels attenuated the association of metformin use with cognitive function. While adjustment for B_{12} levels abrogated the statistical significance of this association, the confidence intervals around the odds ratios overlap substantially, leaving open the possibility that B_{12} levels are unrelated to the association of metformin with cognitive function.

Moore et al. (1) appropriately state that larger prospective studies are needed to substantiate their results. Given the high chance of unrecognized bias related to missing data, their study is hypothesis-generating at best. Unfortunately, the results are already appearing in the lay press (3). The potential of patients self-discontinuing metformin out of unwarranted concern about cognitive decline will likely cause more harm than good.

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Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA

Corresponding author: Mark O. Goodarzi, mark.goodarzi@cshs.org.