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Title: Effect of Metformin on Liver Health in a Sample of Patients with Diabetes

Background

Over 37 million people in the United States are estimated to have diabetes mellitus.[1] Metabolic dysfunction-associated steatotic liver disease (MASLD, previously NAFLD) affects over 70% of individuals with diabetes and is driven by similar underlying pathophysiological mechanisms, such as insulin resistance and metabolic syndrome.[2,3] FDA-approved treatment options for MASLD remain limited, but some diabetes medications have shown promise in managing both conditions.[4,5] Metformin is one of the most commonly used oral medications for diabetes and has effects that could be beneficial for the liver, such as enhancing insulin sensitivity, but studies on metformin and liver health have shown mixed results.[6–10] This study aims to use data from the National Health and Nutrition Examination Survey (NHANES) and propensity score methods to evaluate whether use of metformin is associated with improved metrics of liver health in a large sample of patients with diabetes. The main research question addressed in this study was: Is metformin use associated with lower fibrosis-4 (FIB-4) scores, a metric of liver fibrosis, in patients with diabetes in the NHANES sample?

Methods

This was a cross-sectional study using data collected from NHANES, incorporating cycles from 2013 to 2020. NHANES participants were included in the analysis if they were between the ages of 18 and 79, had a diagnosis of diabetes, and had available data on the outcomes. Participants were divided into a treatment and control group for analysis based on whether they were on metformin or not on metformin, respectively. The primary outcome was score on the FIB-4 index, a validated metric that estimates liver fibrosis using age and common labs, with higher scores indicating increased risk of advanced fibrosis or cirrhosis.[11] Data on covariates, including sociodemographic variables, laboratory metrics, and comorbidities, was also collected to generate propensity scores using logistic regression. Multiple propensity matching techniques were tested, including 1:1 nearest-neighbor matching with and without replacement and 1:1 caliper matching with and without replacement (with a caliper of 0.2). Linear mixed models were used to evaluate the outcomes in matched pairs. For unmatched models, inverse probability of treatment weighting (IPTW) was done using an ATT estimand, followed by a double robust linear regression.

Results

Before propensity matching, the subjects in the metformin group had, on average, higher age, were more likely to be in a higher income category, were more likely to be on other antiglycemic medications, and were less likely to have a history of heavy alcohol use relative to the control group. The best balance in covariates from propensity score matching was achieved with 1:1 nearest neighbor matching strategy with

replacement. This model demonstrated that, on average, subjects who were on metformin had FIB-4 scores that were -0.182 points lower than subjects not on metformin in a matched sample (95% CI: -0.279, -0.086). Similar results were seen in a double robust model using ATT weights, which estimated that subjects on metformin had FIB4 scores that were -0.170 points lower on average (95% CI: -0.260, -0.081).

Conclusions

In this study of NHANES participants with diabetes, metformin use was consistently associated with lower FIB-4 scores, a proxy for liver fibrosis. While the effect size was modest, the direction of association remained consistent across multiple propensity score methods. These findings may suggest a potential liver-related benefit of metformin, but the cross-sectional nature of the study limits causal inference and warrants further longitudinal study.

References

Data Source

The data was downloaded from the Centers for Disease Control and Prevention (CDC) NHANES website at https://wwwn.cdc.gov/nchs/nhanes/default.aspx.

Literature Cited

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