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The primary aim of *World Journal of Diabetes* (*WJD*, *World J Diabetes*) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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LETTER TO THE EDITOR

Non-alcoholic fatty liver disease, diabetes medications and blood pressure

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Abstract

New glucose-lowering agents reduce liver enzyme levels and blood pressure (BP). Whether this finding can be extended to non-alcoholic fatty liver disease (NAFLD) patients, in whom a bidirectional association of NAFLD measures and BP has been also demonstrated, remains by and large unknown.

Key Words: Antidiabetic drugs; Blood pressure reduction; Non-alcoholic fatty liver disease; Sodium glucose cotransporter 2; Alanine aminotransferase; Aspartate aminotransferase

Core Tip: All new glucose-lowering agents reduce liver enzyme levels. Additionally, sodium glucose cotransporter 2 inhibitors can reduce both systolic and diastolic blood pressure (BP) by 3.5/1 mmHg, respectively, while glucagon-like peptide-1 agonist treatment was accompanied by systolic BP reduction of 1 mmHg. Whether this previous finding can be extended to non-alcoholic fatty liver disease (NAFLD) patients, in whom a bidirectional association of NAFLD measures and BP has been also demonstrated, remains by and large unknown.

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TO THE EDITOR

We read with interest the meta-analysis by Fu *et al*[1], which aimed to investigate the changes from baseline of selective liver enzymes, namely alanine aminotransferase and/or aspartate aminotransferase, in patients with non-alcoholic fatty liver disease (NAFLD). Patients were treated with either new glucose-lowering agents [*i.e.*, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor (GLP-1) agonists, and sodium glucose cotransporter 2 (SGLT2) inhibitors] or placebo/other glucose-lowering drugs. Secondary outcomes along with the same comparison were changes from baseline of (1) different measures of body adiposity partly estimated by liver magnetic resonance, and (2) glycated hemoglobin levels. The authors clearly showed[1] that all new glucose-lowering agents reduced liver enzyme levels, whereas measures of body adiposity including body fat composition were at least numerically reduced in all cases. It would be interesting to know the changes of fatty liver index[2-4], which is a more integrated measure of liver damage in NAFLD, and whether new glucose-lowering agents can effectively reduce blood pressure (BP) levels in this pool of studies. The effect of new glucose-lowering agents against placebo on BP levels has been investigated in a pool of outcome trials[5], suggesting that among these agents, only SGLT2 inhibitors can reduce both systolic and diastolic BP by 3.5/1 mmHg, respectively, while GLP-1 agonist treatment was accompanied by systolic BP reduction of 1 mmHg. Whether this previous finding[5] can be extended to NAFLD patients, in whom a bidirectional association of NAFLD measures and BP has been also demonstrated[6], remains by and large unknown.

Beyond the above clinical considerations, we would like to emphasize on some technical issues regarding the meta-analysis by Fu *et al*[1]. First, the authors estimated changes from baseline and not differences after the intervention. Differences from baseline can bias the results in two ways, (1) because of Wilder's principle[7], indicating that reductions are higher from higher baseline levels, and (2) because in randomized studies with a limited number of participants, the levels of a given measure are not identical between treatment arms[8]. Second, another source of bias is the inclusion of placebo-controlled and active-controlled studies[9]. Although placebo is a fair comparator in this type of investigation, active-controls may have reduced the net outcome effect of new glucose-lowering agents. Third, wandering between statistical models (*i.e.*, fixed-effect *vs* random-effects) is not advised in clinical meta-analyses and a random-effects model, when gathering studies from the literature, should always - a priori - be selected irrespectively of the underlying heterogeneity [10].

The study by Fu *et al*[1] is clinically important and suggests that new glucose-lowering agents contribute to a reduction of NAFLD severity, which may partially explain the cardioprotective effect of these drugs on major outcomes[5,11].

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