A combination of metformin and insulin is an effective treatment that benefits the cardiovascular and cerebrovascular system in individuals with type 1 diabetes mellitus

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Abstract

Background

This study aims to further clarify whether there are cardiovascular and cerebrovascular benefits associated with insulin treatment combined with metformin in individuals with type 1 diabetes.

Methods

Electronic databases were searched for randomized controlled trials in which the efficacy and safety of metformin were compared with those of a placebo for the treatment of cardiovascular and cerebrovascular disease among type 1 diabetes patients, and a meta-analysis was conducted.

Results

Thirteen cardiovascular studies were identified. In the metformin group, mean carotid intimal media thickness was significantly reduced by 0.03 mm, ascending aortic pulse wave velocity by 6.3 m/s, descending aortic wall shear stress by 1.77 dyn/cm², insulin daily dose by 0.05 U/kg/d, body weight by 2.27 kg, fat-free mass by 1.32 kg, body mass index by 0.58 kg/m², hip circumference by 0.29 m, and low-density lipoprotein by 0.16 mmol/L. In the metformin group, flow-mediated dilation was increased by 1.29%, glucose infusion rate/insulin by 18.22 µU/µL, and waist-to-hip ratio by 0.02. The metformin group showed no differences in blood pressure, reactive hyperemia index, waist circumference, triglyceride, total cholesterol, high-density lipoprotein cholesterol, or body mass index Z score. For cerebrovascular studies were identified. But none of them had a risk factor assessment.

Conclusions

There is strong evidence supporting wider use of metformin to improve cardiovascular and cerebrovascular disease risk among individuals with type 1 diabetes, not just obese or adults.

Background

The incidence of type 1 diabetes mellitus (T1DM) is increasing annually. Notably, a study of 19 countries showed that only 30% of T1DM patients had HbA1c < 7.5% and that at least 30% of T1DM patients had poor HbA1c (> 9.0%)¹. The complications of diabetes can be reduced by intensive insulin treatment to achieve normal HbA1c. However, the excessive use of insulin is another problem and often reaches 1.5-2 U/kg/d, resulting in weight gain, which may be caused by the increase in low-density lipoprotein cholesterol (LDL) or blood pressure (BP)². In adolescents with T1DM, the adolescent surge of hormones and changes in body composition make HbA1c more difficult to control and can lead to insulin resistance (IR) and excessive weight gain; the body mass index (BMI) of T1DM adolescents has been shown to increase faster than that of nondiabetic adolescents³. IR also accelerates the progression of atherosclerosis⁴.

Atherosclerosis is the basis of cardiovascular disease (CVD), the main cause of death in individuals with T1DM⁵. Even if T1DM patients can maintain a good HbA1c, their risk of cardiovascular morbidity is still three-fold higher than that of the general population⁶. Recent research has found that metformin may improve vascular endothelial dysfunction, which is the first step in the development of atherosclerosis in patients with T1DM⁷. Metformin may reduce carotid intimal media thickness (cIMT) in patients with T1DM⁸. Even if statins are used for 2 to 4 years, they cannot change cIMT in individuals with T1DM⁹. Studies have shown that atherosclerosis exists in children with T1DM¹⁰, but vascular functional and structural disorders can be reversed. The effects of adding metformin to the treatment for T1DM on reducing HbA1c have been inconsistent.

Diabetes raises the risk of ischaemic stroke through increased atherosclerosis and endothelial dysfunction while also leading to a slower and less complete recovery following stroke¹¹. Brain blood vessel dysfunction in diabetic subjects can result in a high level of bleeding following stroke, which worsens prognosis and hinders functional recovery after stroke¹². Metformin has recently been shown to ameliorate many of the negative effects of stroke by acting through AMPK-mediated pathways¹³. Cerebrovascular diseases that already were classified as neurological diseases and no longer belong to CVD after 2018 were separated the statistics and the discussion in this article.

This study aims to further clarify whether the cardiovascular and cerebrovascular system benefits from the addition of metformin to insulin treatment in individuals with T1DM.

Methods

Search strategy and study selection

In this meta-analysis, two of the study authors searched the MEDLINE, EMBASE, and Cochrane Library databases for articles published through 15 July 2020, using the Mesh and text terms “metformin,” “diabetes mellitus, type 1” and “carotid intima thickness, atherosclerosis, lipid profile, vascular function, cardiovascular disease” or “Stroke, transient ischemic attack, cerebral hemorrhage, subarachnoid hemorrhage” to identify randomized clinical trials (RCTs) that compared the efficacy and safety of metformin with those of a placebo for the treatment of atherosclerosis among T1DM patients. We also manually scanned reference lists from trials and review articles to identify other relevant publications¹⁴.

Data extraction

All potentially eligible scientific reports assessing the effects of metformin compared to those of a placebo were identified by two authors. Each full-text article was reviewed by these two authors¹⁴. The data were then extracted, and both authors independently assessed the study quality using a standardized approach. Any disagreement in extracted data was settled by other investigators to reach a final decision. The data extracted included the first author, year of publication, country where the study was conducted, number of participants, number of patients lost to follow-up, mean age of participants, diabetes duration, intervention duration, clinical outcomes, and safety outcomes. Studies were excluded if they were case reports, letters, comments, or editorials or if no quantitative outcomes were reported¹⁵. The primary clinical outcomes of interest were cIMT⁹, reactive hyperemia index (RHI)¹⁶, flow-mediated dilation (FMD)¹⁷, pulse wave velocity (PWV)¹⁸, wall shear stress (WSS)¹⁹, and glucose infusion rate/insulin (M/I)²⁰. The secondary outcomes included lipid profiles, which consisted of total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), and LDL; BP; waist and hip circumferences; HbA1c; BMI; homocysteine(HCY) and total insulin daily dose (TIDD). Safety outcomes included severe hypoglycemic events, diabetic ketoacidosis (DKA) events, and gastrointestinal adverse events.

Data analysis

Two authors independently assessed the risk of bias for each included trial using the Cochrane Risk of Bias Tool for Randomized Controlled Trials and the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions¹⁸. Summary estimates were obtained using a fixed-effects model, and a random-effects model was used when $I^2 > 50\%$. We measured the treatment effect by calculating risk ratios (RRs) with 95% confidence intervals (CIs) for dichotomous data and mean differences (MDs) with 95% CIs for continuous data. All statistical analyses were performed using the Cochrane Review statistical software, Review Manager 5.2.

Results

Description of studies

The electronic searches resulted in the identification of 378 cardiovascular disease records: MEDLINE 185; EMBASE, 136; and Cochrane, 57. After removing duplicates, 103 records remained, and after examination of the titles and abstracts of these records, we eliminated any studies that clearly did not match our inclusion criteria. We obtained full-text copies of the 33 potentially eligible articles and subjected these to further evaluation. We excluded 9 articles because they were controlled clinical trials, not RCTs. Finally, 24 articles were found to be eligible and included in the meta-analysis (Ahmed 2016²¹, Anderson 2013²², Anderson 2016²³, Anderson 2017⁷, Bjornstad 2018²⁴, Burchardt 2013²⁵, Burchardt 2016²⁶, Jacobsen 2009²⁷, Khan 2006²⁸, Lund 2008²⁹, Lund 2009³⁰, Lunder 2018³¹, Nadeau 2015³², Nadeau2016³³, Nadeau 2017³⁴, Nadeau 2018³⁵, Nadeau 2018-2³⁶, Petrie 2016³⁷, Petrie 2017³⁸, Petrie 2017-2³⁹, Petrie 2018⁴⁰, Pitocco2013⁴¹, Wiromrat 2018⁴², Xu 2018⁴³). Twenty-four articles were from 13 different studies published at different times: Nadeau 2015, 2016, 2017, 2018, and 2018-2 reported data from the same study, and thus, we used Nadeau 2018 as a representative publication. In addition, Lund 2008 and Lund 2009 presented a similar situation, and we used Lund 2009 as the representative article; Petrie 2016, 2017, 2017-2 and 2018 reported data from the same study, and Petrie 2017 was selected as the representative paper. Anderson 2016, 2017, and 2013 reported data from the same study, and we chose Anderson 2017 as the representative publication. Finally, Bjornstad 2018 and Wiromrat 2018 reported data from the same study, so we selected Bjornstad 2018 as the representative article. However, the main results of these articles were different, so they were all included (Figure 1). The thirteen different studies included data from 1030 T1DM patients: 555 patients with a combined insulin and metformin treatment and 475 patients with a combined insulin and placebo treatment. Details of the studies included are shown in Table 1.

The electronic searches resulted in the identification of 0 cerebrovascular disease record. We removed the “type 1 diabetes” Mesh and text word to search. The identification of cerebrovascular records was 20: MEDLINE 20; EMBASE, 3; and Cochrane, 1. After removing duplicates, 20 records remained, and after examination of the titles and abstracts of these records, we eliminated any studies that clearly did not match our inclusion criteria. We obtained full-text copies of the 10 potentially eligible articles and subjected these to further evaluation. We excluded 3 articles because they were protocol and 2 articles because metformin was basic drug and 1 article was comment. Finally, 4 articles were found to be eligible and included in the analysis. However, the patients of these 4 articles are not T1DM(Ghotbi2013⁴⁴, Charytan2019⁴⁵, Mellbin2007⁴⁶, Hertog2013⁴⁷). Details of the studies included are shown in Table 2.

Primary clinical outcomes

Four studies reported data regarding the mean cIMT (Anderson 2017, Bjornstad 2018, Nadeau 2018, Petrie 2018). There were 350 patients in the metformin group and 302 patients in the placebo group (Heterogeneity: $P=0.06$; $I^2=59\%$); therefore, a random-effects model was used for the analysis. The overall analysis showed that metformin can significantly reduce the mean cIMT by 0.03 mm ($P<0.00001$). Data describing the effects of metformin on maximum cIMT were consistent (Anderson 2017, Bjornstad 2018, Burchardt 2016, Petrie 2018). The pooled analysis showed a significant difference between the metformin and placebo groups (MD -0.04, 95% CI=-0.07-0.0, $Z=2.08$, $P=0.04$) (Figure 2).

FMD data was provided by Anderson 2017, Lunder 2018, and Pitocco 2013 (heterogeneity: $P=0.004$; $I^2=82\%$). Compared with the placebo, metformin significantly increased FMD by 1.29% ($P=0.02$). The sensitivity analysis determined that the heterogeneity disappeared after the removal of Anderson 2017 ($P=0.19$; $I^2=42\%$). Metformin significantly increased FMD by 2.03% (95% CI=1.12-2.93, $P<0.0001$). Three studies provided data on RHI with different treatment regimens (Nadeau 2018, Lunder 2018, Petrie 2018) (heterogeneity: $P<0.00001$; $I^2=94\%$). Metformin slightly increased RHI by 0.16% ($P=0.45$) (Figure 3).

There were 2 studies that provided data on ascending aortic PWV (AA PWV) (Bjornstad 2018, Lunder 2018) (heterogeneity: $P=0.04$, $I^2=75\%$). Compared with the placebo, metformin significantly reduced AA PWV by 6.3 m/s ($P<0.00001$). Descending aortic PWV (DA PWV) data was provided by Bjornstad 2018 and Nadeau 2018. These 2 studies presented significant heterogeneity ($P<0.0001$; $I^2=95\%$). Metformin slightly reduced DA PWV by 0.22 m/s ($P=0.32$) (Figure 4).

The maximum descending aortic WSS (DA WSS) data were provided by Bjornstad 2018 and Nadeau 2018 (heterogeneity: $P<0.00001$, $I^2=99\%$). The metformin group showed a significant reduction in the maximum DA WSS of 1.77 dyn/cm^2 ($P=0.02$).

M/I data was provided by Bjornstad 2018 and Nadeau 2018 (heterogeneity: $P<0.00001$; $I^2=95\%$). The metformin group exhibited significantly increased M/I by $18.22 \mu\text{U}/\mu\text{L}$ ($P<0.00001$).

Secondary clinical outcomes

Seven studies provided data on T1DD (Anderson 2017, Bjornstad 2018, Jacobsen 2009, Lund 2009, Nadeau 2018, Petrie 2018, Xu 2018), with 418 patients in the metformin group and 367 patients in the placebo group. Heterogeneity was observed among the included studies ($P=0.002$; $I^2=71\%$). The metformin group exhibited significantly reduced T1DD by 0.05 U/kg/d ($P<0.00001$). Metformin significantly reduced daily insulin dosage by 5.22 U/d ($P<0.00001$) (Figure 5).

Eight studies provided data on the body weight of patients (Pitocco 2013, Petrie 2018, Nadeau 2018, Lund 2009, Khan 2006, Jacobsen 2009, Burchardt 2013, Bjornstad 2018), presenting significant heterogeneity ($P=0.001$; $I^2=70\%$); metformin significantly reduced body weight by 2.27 kg ($P<0.00001$). Sensitivity analysis was performed, and heterogeneity disappeared after the removal of Jacobsen 2009 ($P=0.61$; $I^2=0\%$). Metformin significantly reduced body weight by 1.90 kg (95% CI= -2.07 – 1.73 , $P<0.00001$). Eight studies provided BMI data (Xu 2018, Pitocco 2013, Nadeau 2018, Lunder 2018, Lund 2009, Burchardt 2013, Bjornstad 2018, Ahmed 2016) (heterogeneity: $P=0.49$; $I^2=0\%$). Metformin also significantly reduced BMI 0.58 kg/m^2 ($P<0.00001$). Bjornstad 2018 and Nadeau 2018 provided data on BMI Z scores (heterogeneity: $P<0.00001$; $I^2=99\%$). Compared with the placebo group, the metformin group showed no effect on the BMI Z score ($P=0.33$). Furthermore, Bjornstad 2018 and Anderson 2017 provided data on fat-free mass. Heterogeneity was not found ($P=0.31$); metformin significantly reduced fat-free mass by 1.32 kg ($P<0.00001$), as shown in Figure 6.

Eight studies provided TC data (Ahmed 2016, Anderson 2017, Bjornstad 2018, Burchardt 2013, Jacobsen 2009, Khan 2006, Lund 2009, Nadeau 2018). The included studies had significant heterogeneity ($P<0.00001$; $I^2=95\%$). The heterogeneity disappeared after the removal of Lund 2009 ($P=0.35$; $I^2=10\%$), but the findings were still not statistically significant (95% CI= -0.08 – 0.06 , $P=0.79$) (Figure 7). Data on HDL were provided in 8 studies (Ahmed 2016, Anderson 2017, Bjornstad 2018, Burchardt 2013, Jacobsen 2009, Khan 2006, Lund 2009, Nadeau 2018) (heterogeneity: $P<0.00001$; $I^2=81\%$). Compared with the placebo, metformin had no effect on HDL (95% CI= -0.08 – 0.00 , $P=0.05$) (Figure 8). Seven studies provided LDL data (Anderson 2017, Bjornstad 2018, Burchardt 2013, Jacobsen 2009, Khan 2006, Lund 2009, Petrie 2018) (heterogeneity: $P<0.00001$; $I^2=86\%$). Compared with the placebo, metformin significantly reduced LDL by 0.16 mmol/L ($P=0.01$). Sensitivity analysis was performed to determine the heterogeneity after the removal of Lund 2009 ($P=1.00$; $I^2=0\%$). Metformin significantly reduced LDL by 0.11 mmol/L (95% CI= -0.16 – 0.06 , $Z=4.11$, $P<0.0001$) (Figure 9). Data on TG were provided in 7 studies (Ahmed 2016, Anderson 2017, Bjornstad 2018, Burchardt 2013, Jacobsen 2009, Khan 2006, Lund 2009) (heterogeneity: $P=0.003$; $I^2=69\%$). Metformin slightly increased TG by 0.05 mmol/L ($P=0.33$). The heterogeneity disappeared after the removal of Bjornstad 2018 ($P=0.15$; $I^2=38\%$) and Jacobsen 2009 ($P=0.82$; $I^2=0\%$), but the results were still not statistically significant (Figure 10).

Anderson 2017 and Lund 2009 provided data on hip circumference (heterogeneity: $P=0.82$; $I^2=0\%$). Metformin significantly reduced hip circumference by 0.29 m ($P<0.00001$). Five studies provided data on waist circumference (Anderson 2017, Lund 2009, Lunder 2018, Nadeau 2018, Xu 2018). Significant heterogeneity existed among the 5 studies ($P<0.0001$; $I^2=86\%$). Metformin had no effect on waist circumference ($P=0.67$). The heterogeneity disappeared after the removal of Lunder 2018 and Xu 2018 ($P=0.38$; $I^2=0\%$). Metformin significantly reduced waist circumference by 0.36 m (95% CI= -0.53 – 0.18 , $Z=4.02$, $P<0.0001$). Anderson 2017 and Lund 2009 provided data on the waist-to-hip ratio (heterogeneity: $P=0.29$; $I^2=9\%$). Metformin significantly reduced the waist-to-hip ratio by 0.02 ($P<0.0001$) (Figure 11).

Six studies provided data on BP (heterogeneity: $P=0.002$; $I^2=73\%$). Metformin had no effect on BP ($P=0.34$). The heterogeneity among the studies disappeared after the removal of Bjornstad 2018 ($P=0.12$; $I^2=46\%$). The metformin group showed a tendency toward reduced systolic BP ($P=0.12$). The heterogeneity among the studies disappeared after removing Jacobsen 2009 ($P=0.45$; $I^2=0\%$). Interestingly, the pooled analysis showed that metformin significantly reduced the diastolic BP by 2.01 mmHg (95% CI= -2.69 – 1.34 , $Z=5.83$, $P<0.00001$) (Figure 12).

Homocysteine, as a risk factor for stroke, was not mentioned in the 4 articles. These four articles are not systematically analyzed just reviewed. Ghotbi 2013 showed that metformin treatment reduced the rate of nonfatal stroke compared to insulin treatment. Charytan 2019 showed that metformin treatment at baseline was associated with reduced cardiovascular and cerebrovascular complications in patients with diabetes and CKD. Mellbin 2007 showed that the risk for non-fatal myocardial infarction and stroke increased significantly in patients on insulin (HR 1.73, 95% CI 1.26–2.37; $P=0.0007$), whereas this risk was lower among those on metformin (HR 0.63, 95% CI 0.42–0.95; $P=0.03$). Hertog 2013 showed that metformin treatment improved glucose tolerance following cerebral ischaemia in non-diabetic patients, which is a cause of post-stroke damage.

Regarding the incidence of adverse events among patients with T1DM treated with insulin combined with metformin, 6 studies provided data on hypoglycemic events, 5 studies provided data on ketoacidosis, and 6 studies provided data on gastrointestinal adverse reactions, including adverse events experienced by those treated with insulin alone. None of the patients dropped out of treatment due to side effects or the study procedures.

Discussion

The incidence of T1DM complications is as high as 96.5% ⁴⁸. The main cause of death among patients with T1DM is cardiovascular complications, and patients urgently need a program to reduce cardiovascular disease risk. Therefore, we conducted a meta-analysis to further confirm the cardiovascular benefits of adding metformin to the treatment plan among patients with T1DM. We analyzed 13 high-quality RCT studies on the effects of cardiovascular risk factors in T1DM patients and found that insulin combined with metformin significantly reduced the mean and maximum cMT compared with the effects of insulin alone among T1DM patients. The use of cMT as a primary outcome is highly consistent with cardiovascular outcomes, with a positive predictive value

of 96%⁴⁹. This result showed that metformin had a direct effect on preventing the progression of atherosclerosis among T1DM patients, although not by reducing HbA1c because there were no changes in HbA1c in any of the studies.

Another important result was that metformin can significantly improve vascular endothelial function in patients with T1DM. Combined insulin and metformin treatment significantly increased FMD by 1.29%. FMD is considered a very important standard for the noninvasive evaluation of the vascular endothelium and is widely used in the early detection and prognosis evaluation of a variety of cardiovascular diseases¹⁷. The treatment of T1DM with insulin combined with metformin significantly reduced AA PWV by 6.3 m/s. PWV is an indicator that can reflect the degree of vascular sclerosis, and an increase in PWV reflects endothelial dysfunction¹⁸. Endothelial dysfunction is the early manifestation of atherosclerotic plaques before angiography or ultrasound and is the initiating factor of atherosclerosis; moreover, the endothelium is the target organ of cardiovascular and cerebrovascular disease risk factors⁵⁰.

The use of metformin can reduce not only LDL but also the use of statins⁵¹. Some scholars have proposed that in T1DM patients, the risk of CVD is reduced by approximately 20% for every 0.5 mmol/L reduction in LDL⁵². Our meta-analysis showed that metformin reduced LDL by 0.16 mmol/L and reduced the risk of CVD by 6.4%. As seen above, metformin protects vascular endothelial function and reduces LDL level, thus reducing lipid deposition and ultimately reducing cIMT. As a possible mechanism, metformin, via 5'-adenosine monophosphate-activated protein kinase (AMPK) activation, has been thought to directly reduce atherosclerosis and support the molecular effects of statins on cholesterol metabolism⁵³. In addition, metformin can inactivate methylglyoxal through the non-AMPK pathway, improve endothelial function, and inhibit the formation of glycosylation end products⁵⁴.

Insulin combined with metformin treatment in patients with T1DM can significantly reduce weight by 2.27 kg, BMI by 0.58 kg/m², TIDD by 0.05 U/kg/d, daily insulin by 5.22 U/d, fat-free mass by 1.32 kg, and hip circumference by 0.29 m. In addition, metformin reduced the daily insulin requirement by approximately 16%. These findings all show a decrease in central fat. When the data were subanalyzed by sex, only the waist circumference and BMI Z score of women decreased significantly³². Perhaps appetite suppression may partly explain the significant weight loss²⁷. Metformin can significantly increase the M/I by 18.22 µU/µL. These results suggest that metformin continues to improve IR, which is an increasingly recognized factor that contributes to the progression of CVD in T1DM patients⁴. Therefore, treatments targeting IR in T1DM patients have become an effective method for the prevention of cardiovascular diseases.

In the past 10 years, there have been 5 meta-analyses on the efficacy of insulin combined with metformin for treating patients with T1DM. The meta-analysis by Al-Khalifa showed that there is no evidence of improving HbA1c but strong evidence of reducing TIDD and BMI. The combination therapy was deemed as safe⁵⁵. The meta-analysis by Liu (2016) showed that the effect may be different between overweight/obese adolescents and nonobese adolescents and can increase the risk of adverse events⁵⁶. Liu's (2015) meta-analysis showed that metformin can reduce TIDD, weight, and lipid levels. Metformin does not increase the incidence of hypoglycemia or ketoacidosis⁵⁷. Vella (2010) concluded that metformin can reduce TIDD⁵⁸. The meta-analysis conducted by Meng showed that insulin combined with metformin could significantly reduce TC and LDL in T1DM patients¹⁴. Those meta-analyses did not include a marker of poor cardiovascular prognosis. The combination of insulin and metformin was associated with a slight increase in gastrointestinal reactions leading to hypoglycemic events in T1DM patients. Therefore, when adding metformin to the T1DM treatment regimen, it is necessary to closely monitor blood glucose and adjust TIDD in a timely manner to reduce the occurrence of hypoglycemia.

Metformin can improve cardiovascular disease risk factors, which are also risk factors for cerebrovascular disease. However, another risk factor for cerebrovascular disease is hyperhomocysteinemia. Zhang 2016 Meta-analysis suggested that metformin could decrease the concentration of Hcy when exogenous B-group vitamins or folic acid supplementation was given⁵⁹. Therefore, metformin can decrease the risk of stroke and has recently been shown to be capable of improving recovery following stroke⁶⁰. Metformin can improve the neurological function and oxidative stress status of acute stroke patients with type 2 diabetes, and its mechanism may be related to the AMPK/mTOR signaling pathway and oxidative stress⁶¹. The underlying metformin mechanisms include decreasing mitochondrial dysregulation, oxidative stress/reactive oxygen species, blood-brain-barrier breakdown, inflammation of the brain, and neuronal apoptosis⁶⁰. Therefore, there should be more clinical trials to determine whether metformin can be added to improve stroke in T1DM, type 2 diabetes, and Non-diabetic patients, basing on metformin decreasing risk factors of cerebrovascular disease and underlying mechanisms.

Pharmacogenomics must also be considered when patients with T1DM are treated with metformin. The maximum dose of metformin is 2500 mg/d, and a box of metformin (Glucophage) is \$4.30, and the annual cost is \$315.40. The average duration of the included studies was 8.5 months. Metformin is a cost-effective therapy.

Conclusion

Multiple factors proved that metformin can prevent the progression of atherosclerosis among T1DM patients, significantly improve endothelial function, reduce lipid deposition, reduce IR, and ultimately reduce cIMT among T1DM patients. There is strong evidence supporting wider use of metformin to improve CVD and cerebrovascular disease risk among T1DM patients, not just among obese or adults.

Abbreviations

type 1 diabetes mellitus (T1DM), blood pressure (BP), lipoprotein cholesterol (LDL), insulin resistance (IR), body mass index (BMI), cardiovascular disease (CVD), carotid intimal media thickness (cIMT), randomized clinical trials (RCTs), reactive hyperemia index (RHI), flow-mediated dilation (FMD), pulse wave velocity (PWV), wall shear stress (WSS), glucose infusion rate/insulin (M/I), total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), homocysteine (Hcy), and total insulin daily dose (TIDD), diabetic ketoacidosis (DKA), confidence intervals (CIs), risk ratios (RRs), mean differences (MDs), Descending aortic PWV (DA PWV), ascending aortic PWV (AA PWV), descending aortic WSS (DA WSS).

Declarations

Acknowledgements

Not applicable.

Ethics approval and consent to participate

This study was approved by the Second Hospital, Cheeloo College of Medicine, Shandong University(KYLL-2017(KJ)P-0016).

Consent for publication

The consent to publish was obtained from all participants in this study.

Availability of data and materials

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

W.S. designed the article. W.S. and L.X. have made contributions to the acquisition of data. W. W. and S. L. contributed to analysis and interpretation of data. W.S. drafted the work. D. W. reviewed the manuscript. All authors reviewed and approved the final manuscript.

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Tables

Table 1 Details of the cardiovascular disease studies

Study	Country	Metformin dose	Patients (n)	Lost	Follow-up, Months	Age, years	HbA1c, %	Diabetes duration, years	BMI, kg/m ²	Insulin dose	Outcome
Ahmed 2016	UK	1000 mg bid	32	0	2	46±13	7.3±0.9	23±13.6	28.7	44u/d	TC, LDL,
Anderson 2017, 2013, 2016	Australia	1000 mg bid	90	11	12	13.6 ±3.5	8.4	5.2±3.6	/	0.82±0.22u/kg/d	insulin dose, BMI, cIMT, GTN
Bjornstad 2018, Wiromrat 2018	UA	1000 mg bid	48	4	3	16.8±2.6	8.0±3.7	7.8±4.2	25.4±4.4	0.83±0.25u//kg/d	insulin dose, BMI, cIMT
Burchardt 2013	Poland	1000-2550 mg qd	68	16	6	33.6±11.1	9.0 ±1.9	15.9±7.8	29.5±3.2	/	TC, LDL
Burchardt 2016	Poland	1000 ±500 mg qd	84	0	6	33.2±11.5	8.5 ±1.7	at least 5 year	/	0.6±0.16 U/kg/d	cIMT
Jacobsen 2009	Denmark	1000 mg bid	24	1	12	40.4±11.7	8.37±0.20	19.1±10.1	29.2±3.0	56.8±2.9 U/d	TC, LDL, F
Khan 2006	UK	850 mg tid	18	3	4	48±12	8.6±1.4	19±10	31.3±2.6	60±14 U/d	TG, TC
Lund 2008, Lund2009	Denmark	1000 mg bid	100	8	12	46.1±11.6	9.48±0.99	30	26.11±3.55	0.74±0.26 U/kg/d	TC, LDL
Lunder 2018	Slovenia	2000 mg qd	20	0	3	46.4±3.9	7.9 ± 0.2	23.2±4.8	28.0±0.3	/	FMD
Nadeau 2015, 2016, 2017, 2018, 2018-2	UK	2000 mg qd	80	7	3.2	15.9±1.7	9.5±1.3	6.7±3.6	23.5±3.0	1.21±0.24 U/kg/d	RHI, insulin dose, waist circumference, BMI, BP
Petrie 2016, 2017, 2017-2, 2018	Five countries	1000 mg bid	428	101	36	55±8.5	8.0±0.82	34±10.8	28.4±4.3	0.63±0.26 U/kg/d	cIMT
Pitocco 2013	Italy	850 mg tid	42	0	6	46±8	7.24±0.90	9.2±0.7	28.7±2.1	0.61±0.22 U/kg/d	FMD, NM
Xu 2018	China	≤1500 mg qd	17	0	6	12-18	9.22±1.69	/	18.33±1.71	1.03±0.23u/kg/d	HbA1c, B waist circumference, insulin dose

Table 2 Details of the cerebrovascular disease studies

Study	Model	n	Major findings
Ghotbi2013	Overweight patients with T2DM	8192	decreased rate of nonfatal stroke compared to insulin treatment.
Charytan2019	Patients with diabetes mellitus and CKD	4038	Metformin treatment at baseline was associated with reduced cardiovascular complications.
Mellbin2007	type 2 diabetic patients	1181	the risk for non-fatal myocardial infarction and stroke increased significantly in patients on insulin (HR 1.73, 95% CI 1.26–2.37; P= 0.0007), whereas this risk was lower among those on metformin (HR 0.63, 95% CI 0.42–0.95; P= 0.03).
Hertog2013	Non-diabetic patients	40	Metformin improved glucose tolerance following stroke in non-diabetic patients, which is a cause of post-stroke damage.

Figures

Figure 1

Flow chart

Figure 2

The pooled analysis showed a significant difference between the metformin and placebo groups (MD -0.04, 95% CI=-0.07-0.0, Z=2.08, P=0.04)

Figure 3

Three studies provided data on RHI with different treatment regimens (Nadeau 2018, Lunder 2018, Petrie 2018) (heterogeneity: $P < 0.00001$; $I^2 = 94\%$). Metformin slightly increased RHI by 0.16% ($P = 0.45$)

Figure 4

These 2 studies presented significant heterogeneity ($P < 0.0001$; $I^2 = 95\%$). Metformin slightly reduced DA PWV by 0.22 m/s ($P = 0.32$)

Figure 5

Metformin significantly reduced daily insulin dosage by 5.22 U/d ($P < 0.00001$)

Figure 6

Bjornstad 2018 and Anderson 2017 provided data on fat-free mass. Heterogeneity was not found ($P=0.31$); metformin significantly reduced fat-free mass by 1.32 kg ($P<0.00001$), as shown in Figure 6.

Figure 7

The heterogeneity disappeared after the removal of Lund 2009 ($P=0.35$; $I^2=10\%$), but the findings were still not statistically significant (95% CI=-0.08-0.06, $P=0.79$)

Figure 8

Data on HDL were provided in 8 studies (Ahmed 2016, Anderson 2017, Bjornstad 2018, Burchardt 2013, Jacobsen 2009, Khan 2006, Lund 2009, Nadeau 2018) (heterogeneity: $P < 0.00001$; $I^2 = 81\%$). Compared with the placebo, metformin had no effect on HDL (95% CI=-0.08-0.00, $P = 0.05$)

Figure 9

Metformin significantly reduced LDL by 0.11 mmol/L (95% CI=-0.16-0.06, $Z = 4.11$, $P < 0.0001$)

Figure 10

The heterogeneity disappeared after the removal of Bjornstad 2018 ($P = 0.15$; $I^2 = 38\%$) and Jacobsen 2009 ($P = 0.82$; $I^2 = 0\%$), but the results were still not statistically significant

Figure 11

Anderson 2017 and Lund 2009 provided data on the waist-to-hip ratio (heterogeneity: $P=0.29$; $I^2=9\%$). Metformin significantly reduced the waist-to-hip ratio by 0.02 ($P<0.0001$)

Figure 12

Interestingly, the pooled analysis showed that metformin significantly reduced the diastolic BP by 2.01 mmHg (95% CI=-2.69-1.34, $Z=5.83$, $P<0.00001$)