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Impact of metformin on hypertension; current knowledge

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Abstract
High blood pressure is a potential adjustable risk factor for vascular complications of diabetes. Numerous categories of anti-hypertensive medications have proven to effectively reduce these complications. Additionally, metformin, besides lowering glucose and lipid levels, has advantages on vascular blood flow and improving endothelial function. In this review, we investigate the potential benefits of metformin in lowering blood pressure. Previous studies suggested that the administration of metformin to non-diabetic patients could efficiently reduce systolic blood pressure. The whole comparison of the evidence shows that metformin may have small effects on lowering blood pressure; however, this effect is not directly via a change in sympathetic activity. Mechanisms of blood pressure reduction by metformin may be due to its indirect effects on insulin resistance, nephroprotective, cardioprotective, improvement of the sympatric nerve system, and endothelial function.
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Introduction

Hypertension (HTN) is a potentially modifiable risk factor for vascular complications of diabetes. Numerous categories of anti-hypertensive medications have proven to effectively reduce these complications. HTN often coincides with type 2 diabetes mellites (DM), which intensifies its adverse cardiovascular effects up to four times compared to normotensive non-diabetic individuals. In the Framingham heart study, HTN was accompanied by a more than 50% increase in any cardiovascular impediments and all-cause mortality. Therefore, HTN is a powerful inducer of cardiovascular diseases in diabetic patients (1).

According to several guidelines, metformin is the first-line pharmacotherapy for type 2 diabetes, which also has lipid-modifying and cardioprotective advantages, without hypoglycemia or weight gain side effects. The cardiovascular benefits of metformin in diabetes were first proved by the United Kingdom Prospective Diabetes Study (UKPDS) (2).

In addition to lowering glucose and lipid levels, metformin plays a role in improving vascular blood flow and endothelial function. Metformin has been shown to effectively reduce the incidence of stroke in diabetic patients in comparison with sulphonylureas and insulin due to its blood pressure-lowering effect. Therefore, metformin is surprisingly found to modify endothelial function, particularly, endothelium-dependent vasodilatation. However, the contribution of the endothelium in adjusting blood pressure is greatly related to the hemodynamic characterization of metformin (3).

Despite increasing evidence of the vasculoprotective effects of metformin, only a limited number of studies have focused on the role of metformin in improving HTN. In this study, we aim to review the recent literature on the antihypertensive effect of metformin.

Search strategy

To conduct this review, we searched in Web of Science, Elton B. Stephens Company (EBSCO), Scopus, PubMed/Medline, Directory of Open Access Journals (DOAJ), Embase, and Google Scholar, using various keywords including metformin, hypertension, blood pressure, insulin resistance, nephroprotective, cardioprotective, and endothelial function.

Evidence

Treatment with metformin has a protective effect on the pre-hypertensive stages. A study on spontaneously hypertensive rats revealed that increased asymmetric dimethylarginine (ADMA) levels and diminished nitric

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Implication for health policy/practice/research/ medical education

Metformin can reduce blood pressure through several mechanisms including decreasing insulin resistance, improvement of endothelial function, balancing the autonomic nervous system, nephroprotective, and cardioprotective effects.

oxide (NO) are related to HTN development. Metformin is known to help with the recovery of the endothelial ADMA/NO pathways leading to an increase in NO levels and reduction of ADMA, which lower blood pressure in spontaneously hypertensive rats (4).

Using metformin during pregnancy has a protective effect on prenatal and post-weaning periods when HTN might be induced by the high-fat diet. This effect might be explained by the impact of metformin on the kidneys of children treated with high-fructose and post-weaning high-fat diet, comprising the renin-angiotensin system inhibition, oxidative stress reduction, and uric acid level reduction (5).

A retrospective cohort study was directed in patients with type 2 DM and HTN to compare the effect of metformin with sulfonylureas on blood pressure after administration of the medication for one year, which confirmed that sulfonylureas augmented systolic blood pressure, which might be due to weight gain, hyperinsulinemia, and resulting vascular reactivity (6).

A smaller double-blind study conducted by Wulffelé et al on 147 patients with type 2 diabetes who were being intensively treated with insulin revealed that adding metformin to insulin has no significant effect on their blood pressure (7). These results greatly propose that the effects of metformin on cardiovascular disease in type 2 diabetic patients on insulin treatment are likely attributed to other mechanisms such as glucose and lipid control, weight loss, and insulin necessity reduction. Wulffelé et al also conducted a meta-analysis on 41 studies including 3074 patients, which suggested that metformin does not intrinsically affect the blood pressure in diabetic patients (8). Furthermore, Alemi et al in 2018 compared the effect of four classic anti-diabetic regimens on patients' blood pressure, which did not show statistically significant variation in pulse pressure, systolic blood pressure, and diastolic blood pressure (9).

However, a prior study by Hamidi Shishavan et al in 2017, showed that metformin reduces blood pressure in the aorta of spontaneously hypertensive rats via an increase in endothelial-vasodilator mediators, beyond its glucose control (10). Additionally, a retrospective cohort study based on Taiwan's National Health Insurance data (1999–2005) found that metformin administration decreases HTN in lately diagnosed type 2 DM (11).

Administration of metformin during pregnancy is associated with decreased hypertensive disorders of pregnancy in patients with obesity of gestational DM, in comparison with other anti-diabetes medications (12). It is shown that metformin can decrease fructose-induced HTN by reducing vasoconstrictor prostaglandin construction (13).

Some recent meta-analysis studies showed administration of metformin in non-diabetic patients could efficiently reduce systolic blood pressure (by an average of 2.0 mm Hg), particularly in pre-diabetic or obese individuals, however, it does not have a significant effect on diastolic blood pressure (14,15). Despite the recommendation of the American Diabetes Association for the administration of metformin in pre-diabetes to decrease diabetes risk, this medication is seldom prescribed to this at-risk group. It may be due to the FDA has not confirmed metformin use for this group (15).

Some prior experimental results showed that the blood pressure-lowering effects of metformin are often detected in high blood pressure persons (16). Metformin reduces blood pressure by phosphorylation of the sodium-chloride co-transporter (NCC) and increasing sodium excretion in the kidneys (17). In addition, metformin reduces angiotensin II-induced HTN via stimulation of urinary sodium excretion. Deji et al in their experiment on mouse models measured the variation in salt sensitivity by performing the salt loading test through angiotensin II infusion for the duration of two weeks with or without metformin. This finding indicates that metformin administration can preclude angiotensin II-induced salt-loading HTN by activating AMP-activated protein kinase (AMPK) in the kidneys (18).

Mori et al in their study reported that metformin dilates retinal blood vessels in a dose-dependent manner. This vasodilatory effect of metformin is suppressed by compound C (an inhibitor of AMPK) and nitro-arginine (an inhibitor of NO synthase). Hence, metformin acts via the activation of AMPK, and NO has a vital contribution to its vasodilatory response (19). The blood pressure-reduction effect of metformin could be mediated by vascular smooth muscle and reduction of plasma catecholamine levels and afterward increased NO production (20).

Furthermore, metformin reduces nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity in podocytes causing decreased oxidative stress. The decreased oxidative stress and repaired endothelial function by metformin assist in lowering blood pressure in diabetic models. The aberrant endoplasmic reticulum (ER) stress contributes to the advance of angiotensin II-induced HTN. Metformin suppresses angiotensin II-induced ER stress via AMPKα2 activation, which mediates phospholamban phosphorylation. Metformin only applies its activity in lowering blood pressure in circumstances where AMPKα2 is present and ER stress is increased. These supplies suggest an explanation for the controversial effects of metformin on blood pressure (21). Metformin has been verified to weaken salt-induced HTN in spontaneously hypertensive rats, while it does

not influence blood pressure in models with a normal salt diet. The whole comparison of evidence shows that although metformin may have small effects on lowering blood pressure, it does not have a significant direct effect on sympathetic activity. These effects also look related to obesity or pre-diabetes that may be indirectly associated with the weight loss induced by metformin (22).

Suggested mechanisms for antihypertensive effects of metformin

There are some controversies on the antihypertensive role of metformin, which might be due to methodological restrictions, including the lack of monitoring, pre-identified outcome of blood pressure, not using a control group, insufficient blinding, and low power of some studies. HTN results from the imbalance of blood pressure regulatory systems such as the sympathetic nervous system and the renin-angiotensin-aldosterone system. Some experimental studies suggested elevated serum insulin might be related to HTN in some cases, as they noticed a simultaneous reduction of serum insulin levels and blood pressure by using metformin (16).

Several clinical studies have established the effects of metformin on the vascular endothelium contributing to lowering blood pressure, however, some other studies have not shown this effect. Therefore, it appears that the antihypertensive effect of metformin might be independent of its vasculoprotective effects (3). Likewise, Rizzoni et al suggested that the mechanism of endothelial dysfunction is independent of HTN and seems to be more related to the hemodynamic profile (23).

Pulmonary hypertension

It is reported that metformin can ameliorate pulmonary HTN by inhibiting the production of aromatase and estrogen in a manner dependent on AMPK (24). Furthermore, metformin can activate skeletal muscle mitochondrial sirtuin 3 (SIRT3)-AMPK and increase blood adiponectin levels, which may lessen pulmonary HTN associated with heart failure through a series of pathways affecting adipose tissue, muscle, and lung (25).

Conclusion

Metformin has been proven as a vasculoprotective medication, which can control HTN in diabetic patients indirectly via several mechanisms such as decreasing insulin resistance, improvement of endothelial function, balancing the autonomic nervous system, as well as its nephroprotective and cardioprotective effects. Since metformin is an inexpensive and relatively safe medication, it is vital to conduct more widespread studies to compare its long-term impact on blood pressure in different populations such as normotensive and pre-diabetic patients.

Authors' contribution

Conceptualization: SN and SB.
Validation: SN.
Research: SB and SN.
Data curation: SN and SB.
Writing—Original Draft Preparation: SN, SB and BB.
Writing—reviewing and editing: SSK, EAF, BB, SB and LA.
Visualization: SN and SB.
Supervision: SN.
Project management: SN.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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