EXPERT OPINION

Novel therapeutic targets of metformin: metabolic syndrome and cardiovascular disease

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Introduction: Metformin is a widely used drug in the treatment of type 2 diabetes mellitus (T2DM). However, it is becoming an attractive drug to manage patients with pre-diabetes and to possibly prevent cardiac remodeling and fibrosis and heart failure.

Areas covered: In this review, we highlight the novel therapeutic targets of metformin with a special emphasis on cardiovascular disease. We discuss its key mechanisms of action and new signaling pathways that could partially account for its effect. Furthermore, metformin's role in the management of patients with metabolic syndrome is debated, emphasizing its potential to prevent diabetic heart disease. On the other hand, intense research is ongoing to clarify if metformin will be a future drug to target ischemia-reperfusion injury in the setting of myocardial ischemia.

Expert opinion: In the following years, one should look carefully at basic science results to successfully design and conduct clinical trials, emphasizing patients without full-blown T2DM, but who otherwise might have increased insulin resistance. Topics such as the prevention of cardiac fibrosis and heart failure with preserved ejection fraction, the attenuation of ischemia-reperfusion injury on an acute coronary syndrome and the post-myocardial infarction left ventricle remodeling surely deserve a special interest and should be faced as potential therapeutic targets for metformin.

Keywords: cardiovascular disease, heart failure, ischemic heart disease, metabolic syndrome, metformin

Expert Opin. Ther. Targets [Early Online]

1. Introduction

Metformin is a biguanide used for the treatment of type 2 diabetes mellitus (T2DM), mainly because of its insulin-sensitizing effect [1]. It is a widely used drug with proven efficacy, safety and overall good tolerability. The mechanistic exploration of its pharmacodynamics revealed that metformin decreases insulin resistance not only by AMP kinase (AMPK)-dependent pathways but also by AMPK-independent pathways, including mitochondrial effects [2].

Insulin resistance plays a key role in the pathophysiology of metabolic syndrome (MetS), a constellation of cardiovascular risk factors, and T2DM [3]. Those states of insulin resistance increase the risk of cardiovascular disease (CVD), a leading cause of morbidity and mortality worldwide [4]. In the past years there has been a growing body of evidence suggesting that metformin might also have an important therapeutic role in MetS [5] and might exert a cardioprotective effect, especially in ischemic heart disease [6] and heart failure [7].

This review aims to provide a clinical viewpoint of the role of metformin not only in the treatment of MetS and prevention of CVD but also in the management of the

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Article highlights.

- Metformin already has a role in the management of non-diabetic patients, such as patients with metabolic syndrome.
- One of its key subcellular effects is mitochondrial complex I inhibition, changing the cell's energetic balance. Furthermore, downstream signaling includes AMP kinase-dependent and -independent pathways.
- In the recently published GIPS-III trial, metformin did not improve left ventricle function after a STEMI in non-diabetic patients.
- Its cardioprotective role may include the prevention of post-myocardial infarction remodeling and heart failure, the regression of cardiac fibrosis caused by states of pressure overload or insulin resistance and the improvement of ischemia-reperfusion injury.
- The design of randomized Phase II and Phase III clinical trials to address new potential indications for metformin in a non-diabetic population is of uttermost importance, in order to fully understand the potential of this widely available, inexpensive drug.

This box summarizes key points contained in the article.

insulin-resistant patient who already faced a cardiovascular event, emphasizing its direct cardioprotective action.

2. Metformin: mechanisms of action

The overall antihyperglycemic effect of metformin is driven by the suppression of hepatic gluconeogenesis (**Figure 1**). However, a comprehensive understanding of metformin's mechanism of action is still lacking. Its antihyperglycemic effect is largely accounted for by the inhibition of the mitochondrial electron transport chain (complex I) [8]. Furthermore, AMPK, a leading cellular energy sensor [9], is indirectly stimulated by metformin through an increase in the AMP:ATP and ADP:ATP ratios [10]. However, this finding has been challenged in experiments with hepatocytes lacking either AMPK or its upstream activating enzyme LKB1 [11]. In this way, it seems plausible that part of metformin's effect is mediated by AMPK-independent pathways. Indeed, metformin leads to the accumulation of AMP and related nucleotides, inhibiting adenylate cyclase and thereby reducing cyclic AMP levels and downstream signaling via protein kinase A, suppressing glucagon-dependent hepatic gluconeogenesis [12].

Despite its effects on glucose metabolism, it is important to highlight that the long-term beneficial pleiotropic effects of metformin may depend not only on these previously described mechanisms but also on other signaling pathways and mediators not characterized yet (**Figure 1**). For example, the protective role of metformin on the vascular endothelium seems to be partially mediated by increased nitric oxide (NO) production due to AMPK activation of endothelial NO synthase (eNOS) [13] and decreased reactive oxygen species through inhibition of mitochondrial complex I [14].

3. MetS and diabetic cardiac disease – the diabetic continuum

The MetS is a constellation of cardiovascular risk factors that have reached epidemic proportions during the past two decades [15]. It is also known as 'pre-diabetes', including patients who share some cardiovascular risk factors that have a central pathophysiology mechanism, insulin resistance, but who do not have criteria for T2DM diagnosis. It is well established that insulin resistance is central to its pathophysiology, being associated with a proinflammatory, prothrombotic and oxidative state that increases the risk of CVD, with its microvascular and macrovascular complications [3]. According to the current recommendations for the management of non-diabetic patients with MetS, lifestyle changes are mandatory, and metformin is an option to these patients [5]. Indeed, in patients at risk of T2DM, metformin is associated with weight loss and improved lipid profile and insulin resistance, decreasing the incidence of T2DM by 40% [16].

The previously described metabolic dysfunctional status is associated with deterioration of cardiac structure and function. Indeed, myocardial fibrosis plays a pivotal role in cardiac dysfunction in hypertensive and diabetic heart disease [17] and is also present in patients with MetS [18]. Furthermore, experimental studies have shown that diabetic patients have changes in myocardial substrate utilization, impaired calcium homeostasis, mitochondrial dysfunction, increased oxidative stress, activation of the renin-angiotensin-aldosterone and of the sympathetic nervous systems and deposition of advanced glycation end products [19,20]. These neurohumoral and subcellular mechanisms lead to structural and functional changes in the heart, such as increased myocardial fibrosis [21], myocardial steatosis [22], left ventricular hypertrophy [23] and changes in systolic and diastolic function [24]. In humans, diastolic dysfunction is considered the earliest manifestation of myocardial involvement in T2DM [25] and a key component of diabetic cardiomyopathy [19].

Considering the dominant role of insulin resistance in the pathophysiology of the MetS and its cardiac deleterious effects, it seems reasonable to consider that an increase in insulin sensitivity might be associated with a global improvement in the structure and function of the heart. In the past years, it was demonstrated in animal models of insulin resistance and arterial hypertension that metformin prevented cardiac remodeling and progression to heart failure by several mechanisms [26,27]. On the one hand, metformin inhibited cardiac fibrosis in pressure-overloaded mice and collagen synthesis in cardiac fibroblasts by blocking the TGF-β1-Smad3 signaling pathway independently of AMPK activation [28]. On the other hand, metformin attenuated ventricular hypertrophy in rat model of pressure overload, via activation of AMPK, a downstream signaling involving

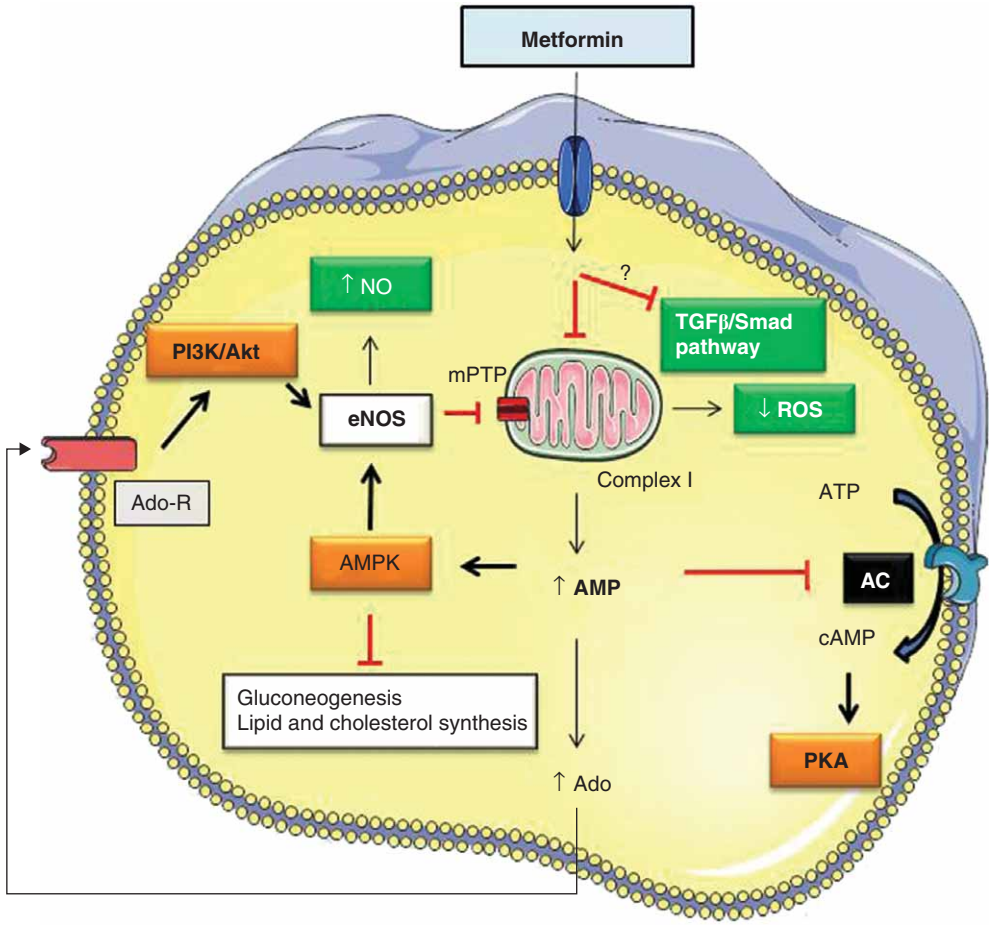

Figure 1. An overview of the mechanisms of action of metformin is shown. After entering the cell, metformin inhibits the mitochondrial respiratory chain (complex I), eliciting a decrease in energy production. Therefore, AMP concentration increases, representing a central mechanism of its intracellular action. The most important mechanisms potentially responsible for its cardiovascular action include: a decrease in ROS production through inhibition of mitochondrial respiratory chain, an increase in NO production due to activation of AMPK and inhibition of TGF-β/Smad pathway (still unknown mechanism).

This figure was produced using Servier Medical Art [65].

AC: Adenylate cyclase; Ado: Adenosine; Ado-R: Adenosine receptor; AMPK: AMP kinase; eNOS: Endothelial nitric oxide synthase; mPTP: Mitochondrial permeability transition pore; NO: Nitric oxide; PI3K: Phosphoinositide-3-kinase; PKA: Protein kinase A; ROS: Reactive oxygen species.

eNOS–NO [29]. Therefore, cardiac beneficial effects of metformin seem to depend on several signaling pathways, suggesting that long-term therapy with this drug may exert a cardioprotective action.

There is considerable interest in understanding if the administration of drugs acting in an earlier phase of the diabetic continuum can improve myocardial structure and function, especially diastolic dysfunction. Considering that changes in diastolic function are already present before the onset of T2DM [30], our group is now conducting a single-center, Phase II, randomized clinical trial to evaluate if the administration of metformin can improve diastolic function in patients with MetS and left ventricular diastolic dysfunction [31].

4. 'Obesity cardiomyopathy': adipokines, insulin resistance and metformin

Obesity has reached global epidemic proportions worldwide, being nowadays a public health concern [32]. Furthermore, recent studies have shown that obesity can directly induce changes in cardiac structure and function, particularly left ventricular hypertrophy and subclinical diastolic dysfunction [33,34]. Several mechanisms may be involved in the obesity cardiomyopathy, such as increased circulating volume and cardiac output [35], induction of a systemic proinflammatory state and secretion of several adipokines [36,37].

The obesity-inflammation continuum is associated with an increase in proinflammatory adipokines (e.g., leptin, resistin,

TNF) and reduced plasma concentration of 'protective' adipokines, especially adiponectin [38]. Adiponectin is a 30 kDa protein that is predominantly secreted by adipose tissue [39], although its levels are inversely correlated with the volume of adipose tissue [40]. Therefore, hypoadiponectinemia is a marker of adipose tissue dysfunction and MetS [41].

After binding to its transmembrane receptors, AdipoR1 and AdipoR2, adiponectin elicits an intracellular cascade that includes activation of AMPK and PPAR-α [42]. The normal intracellular transduction of signal is partially dependent on an adaptor protein, adaptor protein, phosphotyrosine interaction, PH domain and leucine zipper containing 1 (APPL1) [43]. Adiponectin exerts a vasodilatory effect that is mediated by an increase in NO production [44]. This vascular effect is impaired in diabetic rats, not only due to hypoadiponectinemia but also through downregulation of APPL1 and subsequent adiponectin resistance.

Metformin might be able to positively interfere and partially correct the 'adiponectin resistance' present in obesity and MetS. For example, administration of metformin to diabetic rats restored adiponectin levels and APPL1 expression, although it did not have any impact on adiponectin-induced vasodilation. The latter may be explained by downregulated eNOS and adiponectin receptors [45]. In humans, metformin treatment of obese adolescents with insulin resistance improved inflammatory activity by preventing a decrease in adiponectin concentration and eliciting a decrease in the TNF-α concentration [46].

5. Ischemic heart disease

Data from the UK Prospective Diabetes Study (UKPDS) 34 trial showed that metformin decreased diabetes-related clinical events and all-cause mortality not only when comparing to non-pharmacological therapy but also in patients taking insulin or sulfonylureas [47]. Since then metformin is considered the first-line oral drug in the therapy of T2DM. Interestingly, metformin was superior to insulin and sulfonylureas, despite equal reductions in hemoglobin A_{1c}, already suggesting additional cardioprotective actions besides the antihyperglycemic effect.

Animal experiments performed in the past decade revealed that metformin exerted a protective effect against ischemia-reperfusion (I/R) injury in murine hearts [48], attenuated cardiac remodeling and heart failure after myocardial infarction (MI) and even improved survival [49]. Furthermore, diabetic patients already taking metformin when admitted for a ST-segment elevation MI have smaller MI sizes, when compared to diabetics not taking this drug [50].

Metformin exerts its protective effect against I/R injury through several mechanisms. Its administration is associated with the activation of the phosphatidylinositol-3-kinase and Akt, kinases belonging to the reperfusion injury salvage kinase (RISK) pathway [51]. This pathway prevents the opening of the mitochondrial permeability transition pore, which is a pivotal mechanism of I/R injury during early reperfusion [52]. Furthermore, the activation of AMPK and downstream stimulation of eNOS activity may also contribute to the cardioprotective effect of metformin [48]. Interestingly, it was demonstrated in a rat model of I/R injury that metformin-induced reduction in infarct size was critically dependent on adenosine receptor stimulation [53], suggesting that adenosine might be a key mediator of metformin's cardioprotective action. Considering that insulin is known as a cardioprotective agent capable of activating the RISK pathway [54] and recruiting its downstream targets including the phosphorylation of p70S6K, Bcl-2-associated death promoter and eNOS [55,56], metformin might be able to circumvent the loss of this effect in the insulin-resistant myocardium and boost this protective cascade on an ischemic insult.

The enthusiasm for the cardioprotective role of metformin was recently dampened when the Glycometabolic Intervention as Adjunct to Primary Percutaneous Coronary Intervention in ST-Segment Elevation MI (GIPS-III) study showed that when administered for 4 months to non-diabetic patients after a ST-segment elevation MI, metformin was not associated with short-term improved left ventricular function [57]. Future clinical studies should help clarify the importance of metformin's cardioprotective effect against ischemic myocardial injury.

6. Pleiotropic vascular effects

Accumulated evidence shows that metformin exerts several beneficial effects besides those on insulin resistance and cardioprotection. For example, endothelial dysfunction, a key player of the atherosclerosis-inflammation continuum, is ameliorated even with short-term administration of metformin through increased availability of NO and improved endothelium-dependent vasodilation [58]. In this trial including young women with polycystic ovarian syndrome, metformin also reduced arterial stiffness, thereby globally improving vascular function.

Metformin treatment is associated with an improved atherothrombotic and inflammatory blood profile, including reduced levels of plasminogen activator inhibitor type 1, TNF-α and C-reactive protein, as well as increased concentration of adiponectin [59]. Its effect on platelets is still poorly characterized, with studies suggesting decreased platelet aggregation [60], whereas others found no effect on platelet function [61].

The putative antihypertensive effect of metformin also deserves further research. Although older studies suggested that metformin decreased blood pressure [62,63], a recent randomized trial including obese hypertensive individuals without T2DM showed no change in blood pressure in metformin-treated patients [64].

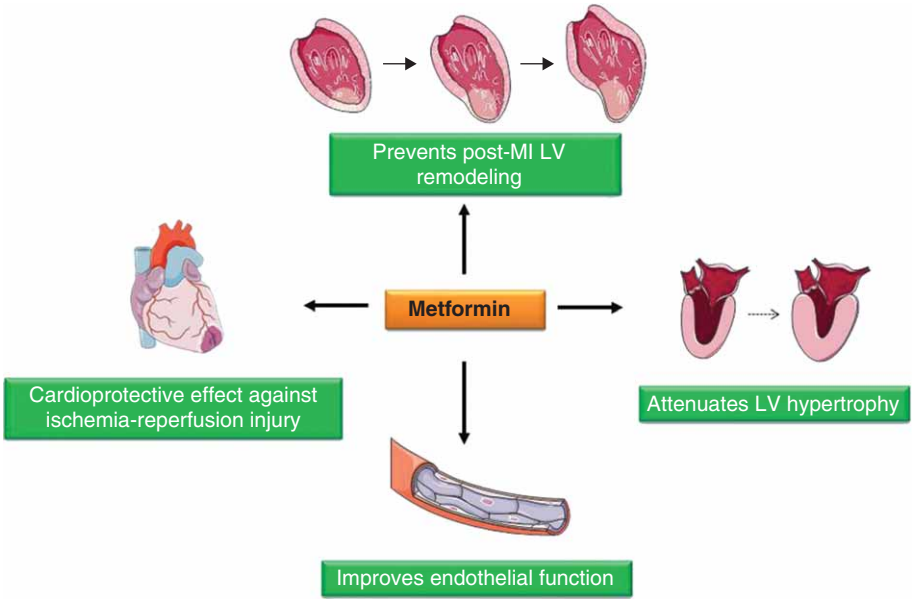

Figure 2. New cardiovascular therapeutic actions of metformin are shown.
This figure was produced using Servier Medical Art [65].
LV: Left ventricle; MI: Myocardial infarction.

7. Conclusion

Metformin started as an insulin-sensitizing drug and is nowadays the first-line drug in the therapy of T2DM. However, the body of evidence accumulated during the past 20 years has shown that metformin has several other beneficial effects on the metabolic profile and cardiovascular system (**Figure 2**, **Table 1**). Indeed, it may not only prevent the progression of a pre-diabetic state to full blown T2DM but it can also prevent the progressive cardiac anatomic and functional changes that accompany the diabetic continuum, contributing to improved systolic and diastolic functions. Furthermore, metformin seems to play a promising role in the prevention of I/R injury associated with acute coronary syndromes – an effect that may be extended to diabetic and non-diabetic individuals. The cellular and subcellular mechanisms responsible for these effects are still being explored, including both AMPK-dependent and -independent signaling pathways. Future research may help unravel novel mechanisms that may represent therapeutic targets of metformin pleiotropic action, further refining its potential to prevent and manage CVD.

8. Expert opinion

Targeting insulin resistance with metformin paved the way for new emerging therapeutic targets for this drug. Basic science has been unraveling the mechanisms that are responsible for its favorable effect in vascular and cardiac functions, improving endothelial function, preventing ischemic heart failure and even reversing cardiac fibrosis. The inhibition of mitochondria as the main effector of metformin's action has recently been challenged by other intracellular mechanisms, including AMPK-dependent and -independent responses. Furthermore, new intracellular actions that may account for its long-term effects such as interference with the protein kinase A and TGF-β signaling cascades are promising findings. In this way, the intracellular effectors of metformin's action represent an interesting field of research that may allow a better understanding of its use as a therapeutic weapon.

Metformin is nowadays viewed as a well tolerated, widely available and inexpensive drug to manage diseases such as MetS and CVD that represent global health problems with epidemic proportions.

However, the scarcity of randomized clinical trials aimed at CVD prevention or treatment and including non-diabetic individuals, as well as the neutral results of some trials (e.g., GIPS-III), have hindered the widening of the therapeutic targets of metformin. Basic science will help us to mechanistically understand the subcellular effect of metformin, possibly discovering new signaling pathways or mediators. Furthermore, robust results in animal models will definitely bring forward the opportunity to translate those findings to humans.

In the following years, one should look carefully at basic science results to successfully design and conduct clinical trials, emphasizing patients without full-blown T2DM, but who otherwise might have increased insulin resistance. Topics such as the prevention of cardiac fibrosis and heart failure with preserved ejection fraction, the attenuation of I/R injury

Table 1. Novel cardiovascular effects of metformin from basic and clinical studies.

Novel cardiovascular effects of metformin	Possible mechanism	Ref.
Animal studies		
Increased endothelial NO production	AMPK activation of eNOS	[13]
Decreased reactive oxygen species production by endothelial cells	Inhibition of mitochondrial complex	[14]
Inhibition of collagen synthesis	Inhibition of TGF-β1-Smad3 pathway	[28]
Attenuation of ventricular hypertrophy in pressure overload	AMPK activation of eNOS	[29]
Protective effect against ischemia-reperfusion injury	AMPK activation of eNOS; phosphoinositide-3-kinase and Akt activation (reperfusion injury salvage kinase pathway); adenosine receptor stimulation	[48,51,53]
Attenuated cardiac remodeling and heart failure after myocardial infraction	Activation of AMPK	[49]

Novel cardiovascular effects of metformin	Ref.
Clinical studies	
Smaller infarct sizes in diabetic patients already on metformin	[50]
Reduced arterial stiffness and improved endothelial function	[58]
Failed to improve short-term left ventricular function after STEMI	[57]
Possible neutral effect on blood pressure	[64]
Improved inflammatory and atherothrombotic blood profile	[59]

AMPK: AMP kinase; eNOS: Endothelial nitric oxide synthase; NO: Nitric oxide; STEMI: ST-elevation myocardial infarction.

on an acute coronary syndrome, and the post-MI left ventricle remodeling surely deserve a special interest and should be faced as potential therapeutic targets for metformin. Clinical investigators may face several challenges in trial design: dose of metformin (low and better-tolerated daily doses such as 500 mg twice daily versus higher doses that may be more effective but also elicit side effects and lead to drug discontinuation), timing of treatment administration (especially in trials addressing the attenuation of I/R injury or the prevention of cardiac fibrosis and heart failure in insulin-resistant patients), need for robust surrogate end points because of the low number of clinical events in the target population and many others. Thoughtful trial design will be challenging but may bring forward positive studies that have potential to change clinical practice.

The interplay among insulin resistance, MetS and cardiac fibrosis and the potential therapeutic role of metformin in this continuum are the active fields of research in the topic. Insulin resistance and MetS are associated with cardiac fibrosis and subclinical diastolic dysfunction. More interestingly, changes in diastolic function are not only typical of diabetic cardiomyopathy but also already present before the onset of diabetes, which reinforces the hypothesis that diastolic dysfunction is mainly associated with the state of insulin resistance and not only to sustained hyperglycemia. An ongoing clinical trial from our center will determine if insulin sensitizers, such as metformin, can improve diastolic function and provide cardioprotection.

In conclusion, the MetS and CVDs are novel therapeutic targets of metformin. Refining our knowledge of metformin's pleiotropic action, including its short- and long-term effects, will definitely need basic and clinical research that may extend the therapeutic indications of this widely available drug, in a global effort to prevent and manage CVD.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents, received or pending, or royalties.

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