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Review Article

Challenge Cardio-Renal Complications in Diabetes - Help is Coming from an Old Friend!

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Abstract

Diabetes Mellitus (DM) a disease of epidemic-like character and one major challenge of the health system, especially in the industrialized world. The progression of this metabolic disorder is often associated with the development of different macrovascular pathologies, such as cardiovascular disease and microvascular complications, such as diabetic retinopathy and nephropathy. Therefore, monitoring of disease development and progression as well as the improvement of existing and development of novel therapeutic treatment options for DM patients is of immense importance for public health care. Metformin is the first line therapeutic option for DM patients because of its significant and reliable anti-diabetic and anti-hyperglycemic effects. Moreover, it was shown to exhibit diverse cardio- and nephron-protective propertiesin the context of diabetes-associated macro- and microvascular complications. In this manuscript, we will summarize and discuss major issues of DM and its associated complication in the context of therapeutic treatment options and other important aspects, such as disease monitoring.

Keywords: Diabetes mellitus; Microvascular; Macrovascular; Complications; Therapy

Abbreviations

DM: Diabetes mellitus; ER: Endoplasmic Reticulum; AMPK: AMP-activated Kinase; mTOR: Mammalian Target of Rapamycin; EMT: Epithelial-to-Mesenchymal Transition

Introduction

Diabetes Mellitus (DM) is a metabolic disease with epidemic-like character and is one of the most important health problems in the industrialized world [1,2]. The development of various macrovascular pathologies, such as myocardial infarction or stroke and microvascular complications, such as diabetic retinopathy, neuropathy, and nephropathy, are often closely related to the progression of DM [1,3-7].

In many cases, abovementioned macro- and microvascular complications were triggered or mediated via endothelial and vascular dysfunction in DM patients [8]. Several molecular biological processes contribute to the pathogenesis of these DM-associated complications and pathologies, e.g. in the cardiovascular or renal system, such as increased Endoplasmic Reticulum (ER) stress, autophagy, oxidative stress, fibrosis, and modulation of intracellular signal transduction [6-9].

Besides monitoring of disease development and diabetic patient education [10,11], therapeutic interventions, e.g. via life style changes or pharmacotherapy are of immense importance to respond to this important epidemic health problem [6,11-14]. Beside a change of life style, metformin is the most prominent therapeutic option for the treatment of DM patients [15-17]. This drug mediatesanti-diabetic and anti-hyperglycemic effects [18]. Moreover, metformin was found to induce various cardio- and nephro-protective properties in the context of DM [6,15-19].

In the following parts of the manuscript, we will summarize major issues of DM and diabetic macro- and microvascular complication. Moreover, we will discuss important therapeutic treatment options and other important aspects, such as disease monitoring in this context.

Metformin

Metformin is an oral hypoglycemic drug that is in first-line position in the pharmacotherapy of DM [15,17]. This biguanide derivate was first synthesized more than 80 years ago, used in clinical trials and DM therapy since 1950s and found to be safe with almost no known significant adverse effects until today [6]. It acts as anti-diabetic drug via increasing peripheral glucose utilization, and peripheral insulin sensitivity as well as by reducing intestinal glucose absorption and hepatic glucose generation [6]. Moreover, metformin was found to increase weight loss in obese subjects [20], which is of immense importance to reduce the risk of DM development as well as progression of overt DM in patients [21]. Beside anti-diabetic properties, this biguanide derivate was demonstrated to exhibit beneficial effects regarding macro- and microvascular complications of DM [6]. In this context, treatment of DM patients with metformin reduced the risk of cardiovascular disease as well as of the development of renal pathologies [22,23].

Even if metformin is a well-tolerated anti-diabetic compound with additional cardio- and reno-protective effects [6,22,23], there are concerns regarding the use of this drug in diabetic patients with severe renal failure, due to some few case studies suggesting that metformin may cause lactic acidosis in those patients [24,25]. This let to sparsely science-based opinion that metformin is contraindicated

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for the treatment of patients with severe renal pathologies [25,26]. In contrast, the risk of lactic acidosis development by metformin treatment of diabetic patients with DM-associated renal pathologies was proven to be very low [6,27]. Combined with the fact that metformin exhibits various cardio- and nephro-protective properties [6,22,28], this led to a growing demand for a revision of the therapeutic guidelines for metformin use in diabetic patients with DM-associated renal pathologies [23].

Cardio-protective effects of metformin in DM

DM-associated dysregulation of pathophysiological-relevant processes, e.g. modulation of cell signaling, induction of oxidative stress, reduced autophagy, and fibrosis play a crucial role in the development of macrovascular complications in DM, such as cardiovascular disease [8,16]. In this context, several studies showed that metformin mediated cardio-protective effects via modulating these processes [16,19,28].

Modulation of signaling via AMP-activated Kinase (AMPK) and its downstream effectors, such as mammalian Target Of Rapamycin (mTOR) plays a central role for the pathogenesis of diabetic cardiovascular complications [16,29]. In this context, it was clearly demonstrated that signaling via AMPK and mTOR is directly involved in the control of pathophysiological processes, such as induction of oxidative stress and reduction of autophagy [29,30]. Metformin was depicted to induce AMPK activity under diabetic conditions [15,31]. In this regard, Hu and colleagues showed that metformin induced the AMPK phosphorylation in cardiomyocytes, which consequently led to reduced oxidative stress and diminished cardiomyocyte injury under hyperglycemic conditions *in vitro* [31]. This anti-oxidative effect of metformin was also found in human endothelial cells under hyperglycemic conditions [32]. Beside its anti-oxidative effect, metformin was depicted to mediate anti-apoptotic as well as anti-fibrotic effects [33]. Picatoste and colleagues showed metformin treatment of cardiomyocytes to diminish hyperglycemia-induced cardiac cell apoptosis and fibrosis *in vitro* [33].

Beneficial effects of metformin on oxidative stress, autophagy, and cardiac fibrosis were verified *in vivo* using appropriate diabetes models as well as in human studies in the context of DM and associated macrovascular complications [9,16,22,33-35]. Xie and colleagues demonstrated metformin treatment of diabetic mice to ameliorate major characteristics of diabetic cardiomyopathy, which were increased oxidative stress, reduced cardiac autophagy as well as diminished cardiac function [34]. They showed that this was mediated by metformin-induced AMPK phosphorylation [34]. In line with these findings, He et al. also depicted that metformin-induced activation of AMPK, increased cardiac autophagic activity and reduced cardiac fibrosis in another mouse model of DM [35]. In another experimental setting, Picatoste et al. demonstrated that metformin decreased cardiac fibrosis and reduced cardiac cell death in diabetic rats [33]. These findings were substantiated by studies in DM patients in the context of cardiovascular complications [9,16,22,28,36]. Formoso et al. showed in DM patient's pharmacotherapy with metformin to reduce oxidative stress [28]. In 2015, Fung and colleagues found that metformin treatment as monotherapy reduced the number of cardiovascular disease events as well as all-cause mortality in Chinese diabetic patients [22]. In line with these observations, Cheng and colleagues demonstrated in 2014that treatment of DM patients with metformin was associated with reduced risk for stroke in those patients [36].

Together, these findings demonstrate that metformin mediates various protective effects in diabetes-associated macrovascular complications, such as diminished oxidative stress, increased autophagic activity, and reduced cardiac fibrosis. These processes were found to be mediated - at least in part - via AMPK activation under diabetic conditions. These findings suggest that the use of metformin may be a potential therapeutic option for the treatment of diabetes-associated macrovascular pathologies, such as cardiovascular disease in DM patients.

Metformin mediated nephro-protective effects in DM

Diabetic nephropathy is one of the most important diabetes-associated microvascular complications often resulting in end-stage renal disease in DM patients [15,37]. This renal pathology is characterized by the several pathophysiological-relevant processes, such as development of albuminuria associated with the loss podocytes, renal damage and loss of renal functions as consequence of progressive glomerulosclerosis, and tubulo intestinal fibrosis [15,37,38]. There are several underlying mechanisms consequently leading to the development and progression of diabetic nephropathy, such as modulation of AMPK and mTOR signaling, increased oxidative stress, ER stress and renal fibrosis [6,15,37].

Hyperglycemic conditions, such as found in DM lead to reduced phosphorylation of AMPK and increased mTOR activity [15,30]. Modulation of signaling via these factors were depicted to control different pathophysiological-relevant processes, such as oxidative stress, autophagy or podocyte loss in the context of DM-associated renal pathologies [6,15,30]. Lee et al. showed in 2007 that hyperglycemia reduced AMPK phosphorylation, which was followed by elevated mTOR activation in rat podocytes *in vitro* [39]. As functional consequence, this led to modulation of gene expression in these renal cells [39]. Substantiating this, we recently demonstrated comparable effects in high glucose-treaded human podocytes, too [15]. Moreover, modulation of AMPK/mTOR signaling was associated with modulation of podocyte viability and gene expression in our experimental setting [15].

In the last decades, metformin was demonstrated to mediate various reno-protective effects under diabetic conditions, including pro-survival effects, anti-oxidative activities, and anti-fibrotic processes. This was often mediated via induced AMPK signaling and modulation of downstream effectors, e.g. mTOR [15,23,26,39]. In 2007, Lee et al. found pharmacological AMPK activation to inhibit high glucose-induced mTOR phosphorylation and modulation of gene expression in rat podocytes [39]. In line, we also demonstrated metformin treatment of human podocytes to restore hyperglycemia-induced reduction of AMPK phosphorylation and elevation mTOR phosphorylation [15]. Consequently, metformin led to increased podocyte survival under high glucose conditions [15]. These findings were further strengthened by *in vivo* studies of different working groups in the context of diabetes-associated renal complications [37,40-42]. In 2012, Kim and colleagues showed that application of metformin to diabetic rats led to increased renal AMPK activation, reduced oxidative stress as well as diminished loss of podocytes and renal functions in this model [40]. In another rat model of

diabetic nephropathy, Takiyama et al. demonstrated that metformin treatment significantly reduced renal tubular fibrosis [41]. This was further substantiated by findings of Louro et al., which depicted that pharmacotherapy with metformin prevented renal injury in diabetic Goto-Kakizaki rats [42].

As mentioned before, increased ER stress is acrucial process in the context of diabetic nephropathy [37,43,44]. Kim et al. demonstrated that hyperglycemia induced ER stress in human renal HK-2 cells [43]. In this context, they also found that administration of metformin to these renal cells abolished hyperglycemia-induced ER stress *in vitro* [43]. In line with these data, Lee and colleagues also showed metformin to increase AMPK phosphorylation and to reduce renal ER stress *in vitro* and *in vivo* [44]. The ER stress-reducing effect of metformin was verified in different further experimental settings *in vitro* and *in vivo* [6, 37].

Renal fibrosis, which plays a major role in the pathogenesis of diabetes-associated renal pathologies, is characterized by Epithelial-to-Mesenchymal Transition (EMT) as well as by extensive generation and deposition of extracellular matrix proteins [6,45]. In the context of diabetic renal pathologies, it was shown by several groups that metformin mediated EMT-diminishing as well as anti-fibrotic effects [46,47]. In 2015, Thakur et al. demonstrated that metformin abolished EMT by induction of AMPK activity in transforming growth factor-β-stimulated primary human proximal tubular epithelial cells. [46]. Substantiating this, Lee et al. showed in 2013 that metformin treatment of renal HK-2 cells increased AMPK phosphorylation and diminished hyperglycemia-induced EMT [47]. These findings are in line with the results of Louro and colleagues [42]. In 2011, they found that metformin blocked EMT and reduced renal fibrosis in diabetic rats *in vivo* [42].

Metformin was also demonstrated in clinical studies to mediate nephro-protective effects in DM [48,49]. In 2000, Amador-Licona and colleagues showed that pharmacotherapy of DM patients with metformin restored diabetes-associate microalbuminuria and led to reduced blood pressure [48]. Some years later, Pan et al. substantiated these finding. They also found metformin application to diminish renal albumin excretion and to reduce blood pressure in DM patients [49].

Together, these studies demonstrate that metformin exhibits various nephro-protective and beneficial properties, such as anti-oxidative, anti-fibrotic, and autophagy-inducing activities via modulating AMPK-dependent signaling in the context of DM-associated renal pathologies. Therefore, these findings suggest that this well-known and time-honored drug may represent a new pharmacotherapeutic treatment option for patients with DM-associated renal complications, such as diabetic nephropathy.

Conclusion

Several micro- and macrovascular complications can be associated with DM, such as cardiovascular or renal pathologies [4,8,45]. Metformin, a longstanding, intensively studied, inexpensive, and well-tolerated drug, is in first-line position in the pharmacotherapy of DM [15,17]. Besides its anti-diabetic actions, metformin was found to mediate various additional cardio- and nephro-protective effects, including anti-oxidative, anti-fibrotic, and autophagy-inducing activities [16,23]. At the same time, this established drug exhibits almost no significant adverse effects [16].This leads to the interpretation that metformin's benefits predominate its rare and only potential risks in the context of DM and diabetes-associated cardio-renal complications [6,27].

Currently, studies are planned and/or already started dealing with the role as well as the safety of metformin in other pathophysiological-relevant settings, such as in the context of metabolic disease or cancer [6,21]. Such studies will consequently lead to a better mechanistic understanding and deeper insights into metformin`s additional potential beneficial effects in these pathologies. Perspectively, this may offer a wider use of this inexpensive and well-tolerated drug, not only in cardiovascular and renal complication of DM, but also in other pathologies, such as in other metabolic diseases and in cancer.

To put it in a nutshell, the aforementioned findings and evaluations indicate metformin to be a potential novel and potent pharmaco therapeutic treatment option for patients with DM-associated cardiovascular and renal pathologies, such as cardiovascular disease and diabetic nephropathy. However, further studies are necessary to analyse and evaluate the precise mechanism of action of metformin as well as its benefits and potential risks in the context of micro- and macrovascular complications in DM.

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