**Review Article**

Influence of Metformin on Age Related Macular Degeneration (AMD)

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**Abstract**

Metformin is the most commonly prescribed antihyperglycemic drug as first-line therapy in type II diabetic patients. In recent years, evidence is increasing that metformin has beneficial effects beyond its classical antihyperglycemic way of action. Those effects include anti-inflammation, anti-oxidation, anti-aging, anti-angiogenesis, anti-neoplasia, anti-apoptosis and neuroprotection. The complex pathophysiology of age-related macular degeneration (AMD) includes age-related changes of the retinal pigment epithelium (RPE) and Bruch’s membrane. An inflammatory and oxidative damage component have also been described. The dry form is especially characterized by loss of retinal neurons (geographic atrophy) and the wet form is characterized by pathological neovascularization. Not surprisingly, an increasing number of reports about beneficial effects of metformin on AMD have been published in the last years. A first prospective trial investigating the effect of metformin on dry AMD is ongoing with estimated results by the end of 2024. In this review, the current knowledge about the association of metformin and AMD is summarized.

**Keywords**: metformin, age related macular degeneration retina, insulin, diabetes, aging, drug therapy, AMPK-pathway

# **INTRODUCTION**

Metformin is one of the most commonly used oral antidiabetic drug. Classically, it is used in non-insulin-dependent type 2 diabetic patients and in most of the cases as the first oral antidiabetic medication. Metformin inhibits the formation of glucose in the liver and improves glucose turnover in the periphery (the muscles) of the body, thereby lowering the blood glucose level (1,2).

There is increasing evidence that metformin may exert several beneficial effects beyond its original antidiabetic function (3–5). In summary, in vitro and in vivo investigations report anti-angiogenic, anti-inflammatory, anti-oxidative, anti-apoptotic, anti-aging and neuroprotective effects of metformin (6,7). Most of these effects also play a crucial role in many retinal diseases such as diabetic retinopathy (DR), age-related macular degeneration (AMD), glaucoma, uveitis or inherited retinal dystrophies as retinitis pigmentosa.

AMD is a vision-threatening disease of the elderly population worldwide with increasing prevalence. Wong et al. calculated an increase from 196 million affected people in 2020 to 288 million affected people in 2040 (8). Together with diabetic retinopathy and glaucoma, AMD accounts for the majority of blindness cases in developed countries. In Germany, for example, it is estimated that AMD is responsible for up to 50% of blind people. (9)

The main risk factor for AMD is age. However, a history of smoking, hyperlipidemia, ethnicity, lifestyle and family history (genetic component) also play a role (10,11). Late-stage AMD can be divided into two forms, the dry, non-neovascular form and the wet, neovascular form. The non-neovascular form of late AMD is characterized by the presence of geographic atrophy in the macular region. In atrophic regions, outer retinal tissue, including the photoreceptor cells, is lost. This leads to a permanent and progressive vision loss as the lesions often advance over time (10). The neovascular form of late AMD is characterized by profound visual symptoms that can aggravate rapidly due to leakage and accumulation of fluid and/or blood in the macular region. If left untreated, fibrosis and permanent vision loss are the consequences (10). Treatment options are only available for neovascular AMD. Intravitreally injected anti-VEGF agents are the standard of care to antagonize pathological neovascularization and the leakage of blood or fluid into the retina.

In the last years, an increasing number of scientific publications report about several potential associations of metformin with the course of the disease. This is true for both the development and the treatment of AMD. In this review, we summarize the current knowledge about these associations and the potential underlying (patho)physiological mechanisms.

# **METHOD**

Systematic literature search was performed using the PubMed library. The search term “metformin age-related macular degeneration” revealed a total of 35 publications (search was performed on July 20th 2022). After screening of titles and abstracts, 22 publications qualified as being suited for the topic of this review. Further database searches with adjusted search terms (metformin AMD, metformin macular degeneration pathways, etc.) did not reveal any further relevant articles.

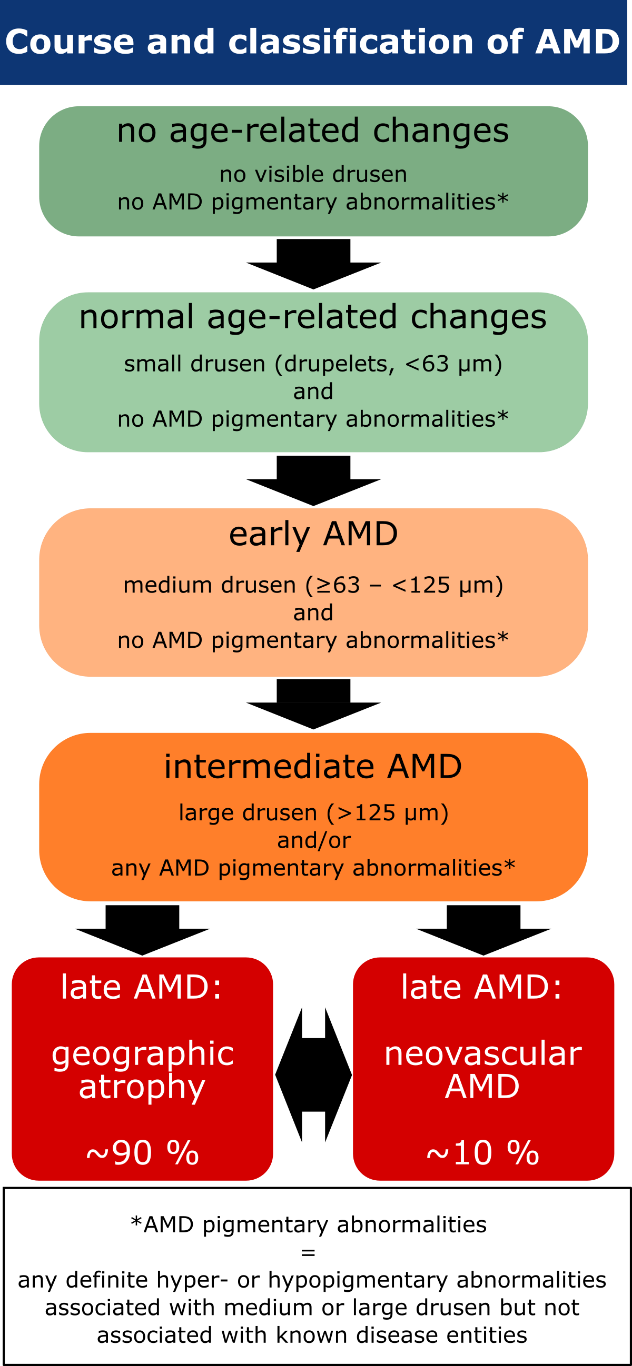
Additional publications have been included for the introductory part as well as for the background part on the pathophysiology of AMD and on the mode of action of metformin. These publications were identified by direct database search as well as by backward citation searching.

# **MAIN TEXT**

## **AMD**

AMD is a progressive, multi-factorial disease with a complex pathophysiology which is probably not fully understood in all its details until today. It is well known that age-related changes as well as environmental influences, a certain genetic disposition and inflammatory processes play a role (11).

Clinically, AMD is classified into an early, an intermediate and two forms of late stage AMD: the dry, non-neovascular and the wet, neovascular form (Figure 1) (12). Small drusen are the earliest precursor signs of AMD that usually do not cause any symptoms. Early and even intermediate AMD may have no or only minimal symptoms (10). Possible symptoms of early and intermediate AMD are subtle distortion (metamorphopsia), increased blurring and decreased contrast sensitivity. Late, neovascular AMD, however, has more profound visual symptoms that can aggravate more rapidly. Distortion is more severe and/or large central scotoma or blind spot can occur due to hemorrhage or fluid accumulation. Late, non-neovascular AMD is characterized by progressive central vision loss due to degeneration of the retinal pigment epithelium (RPE) and the photoreceptor cells, referred to as geographic atrophy (GA) (11).



**Figure 1:** Classification and course of age-relate macular degeneration (AMD). The earliest precursor sigsn of AMD are small drusen that are classified as normal age-related changes. Early AMD is characterized by the presence of medium drusen but the absence of AMD pigmentary changes which are defined as any hyper- or hypopigmentary abnormality. Intermediate AMD shows large drusen and/or the presence of any AMD pigmentary abnormalities. The late stages of AMD are its two distinct forms: neovascular AMD (wet AMD) and geographic atrophy (dry AMD) with the latter being the more common form. Both forms may merge into one another or be present simultaneously. (modified from Ferris et al. (12))

## **AMD - treatment options**

Approved treatment is currently only available for the neovascular form. Standard of care is the intravitreal injection of anti-VEGF agents to antagonize the formation of pathological neovascular vessels thereby reducing retinal damage by sub- and/or intraretinal fluid or blood accumulation (13). Additionally, larger subretinal hemorrhages can be treated by surgical intervention to eliminate the subretinal blood mechanically (14).

The non-neovascular form remains untreatable until today, although efforts are made to find treatment options that at least slow down the progression of the disease (15). Possible targets are the underlying pathophysiological mechanisms that cause the central retinal atrophy. Possible treatment options include nutritional supplements, anti-inflammatory drugs, reduction of oxidative stress, neuroprotection and improvement of choroidal blood flow (15). Another, non-drug mediated therapy has shown promising results for intermediate dry AMD. Photobiomodulation was used to stimulate the retina at a cellular level using certain wavelengths of light (16). As a result, the cellular metabolic function at the level of the mitochondria is activated and stabilized and cellular proliferation and cytoprotection is promoted. Very recently, data of the LIGHTSITE III trial were communicated and showed functional effects by improving the best corrected visual acuity (BCVA) and anatomical effects by cessation of drusen deposition (17).

## **Risk factors and pathophysiology of AMD**

As mentioned above, the pathophysiology of AMD is complex and several risk factors are associated with this disease. As a neurosensory tissue, the retina, especially the photoreceptor cells, are metabolically highly active. This requires a constant balance between breakdown of metabolic waste products and supply of necessary nutrients, including oxygen. In the healthy retina, the RPE with its tight contact to the photoreceptor cells, Bruch’s membrane and the choroidal vasculature executes this important task (18). The monolayered RPE with its tight junctions together with Bruch’s membrane as physical support and as a selective diffusion barrier form the blood-retina-barrier (BRB) which precisely regulates the passage of ions, water, nutrients, proteins and oxygen (19). Any change to this sensitive interface, irrespective of its cause (e.g. age, disease, environmental factors), will affect the precise metabolic balance (11,19).

The three main risk factors for AMD are age, environmental risk factors and genetic predisposition. Age itself has an influence on the viability of both the RPE cells and Bruch’s membrane (11). Age has several negative effects on many intracellular structures of the RPE cells, finally leading to changes of RPE metabolism (11). Similarly, Bruch’s membrane suffers from age-related changes, such as thickening and other structural changes that change its permeability. Altogether, age-related changes negatively influence the integrity of the RPE/Bruch’s membrane interface leading to accumulation of debris that ultimately leads to the formation of drusen (11). According to Anderson et al. local inflammation as a response to debris accumulation plays a critical role in the formation of drusen (20). Analyses of the composition of drusen have shown, that they are composed of lipids, polysaccharides, glycosaminoglycans and proteins (20–22). Additionally, many proteins showed oxidative modifications, supporting the hypothesis that oxidative stress is a further contributor to the pathophysiology of AMD (22).

The most important environmental risk factors are smoking and diet. Smoking increases the risk to develop AMD by two- to three-fold. Moreover, there is evidence that there is a dose-dependent association as well as a reversibility in case of quitting smoking (23). Regarding an individual’s diet, healthy forms, e. g. the mediterranean diet, are associated with a reduced risk due to high content of antioxidants and vitamins (11). In contrast, high fat or high glucose/fructose diets represent a significant risk factor for AMD. Both direct influences of the nutritional components as well as more indirect influences like dysbiosis of the gut microbiota are thought to be associated with AMD formation. The latter leads to a kind of systemic low-grade inflammation (24).

To date, the largest study of the genome-wide association of AMD revealed 52 gene variants across 34 loci (25). 45 out of 52 were classified as common variants, the remaining 7 as rare variants. Furthermore, the analyses showed that the genetic risk is shared between the neovascular and the non-neovascular form of AMD except for one genetic variant that seems to be exclusive for neovascular AMD (25). Further enrichment analyses narrowed down the following molecular mechanisms that could be affected by the identified gene variants: lipid metabolism, extracellular matrix organization and assembly as well as the complement pathway (25). The possible role of the complement system in the pathophysiology of AMD was recently reviewed by Armento et al. (11). In summary, increasing evidence supports the involvement of the activation of the alternative pathway of the complement system, both in a local fashion as well as on a systemic basis. The complement system is part of the innate immune system. Its main functions are the recognition and removal of pathogens, debris and dead cells. These functions are tightly regulated by about 50 proteins that are part of the complement cascade (11,26). Activation of the complement cascade can occur via three pathways: the lectin pathway, the classical pathway and the alternative pathway. Both the lectin and the classical pathway require recognition of counterparts on pathogen surfaces. On the contrary, the alternative pathway is continuously active and its overactivation has to be prevented constantly to maintain tissue homeostasis and to avoid unnecessary inflammation and tissue damage (11).

The crucial anatomic site where AMD pathophysiology begins is the complex of RPE cells, Bruch's membrane, and the choroid. In the healthy retina, this complex does not only mediate the precisely regulated exchange of nutrients and metabolic waste products, but it also inhibits the activation of the alternative pathway of the complement system. As soon as the AMD pathophysiology has been triggered through one or more of its risk factors, normal function of the complex is unbalanced. Consequently, both the integrity of RPE cells and Bruch’s membrane becomes more and more impaired. This leads to a cascade of events that disturb retinal homeostasis: accumulation of metabolic end products, oxidative stress, activation of the complement system thereby inducing local inflammation and cell senescence. Eventually, the blood-retina-barrier breaks down and degeneration of the RPE occurs. Ultimately, irreversible damage to the macular photoreceptors occurs, whether it is the non-neovascular or neovascular form of AMD (11,26,27).

## **Metformin**

Metformin is a synthetic derivative of the naturally occurring galegine from the plant *Galega officinalis* (1). Chemically, metformin is a biguanide consisting of two coupled guanidine molecules with some additional substitutes. As a derivative of a naturally occurring molecule, metformin has not been designed to target specific pathways, nor did it go through the regulatory process of preclinical and clinical trials which are mandatory today. After its safety and efficacy had been established, metformin has been used as glucose-lowering agent since the 1950s (1). FDA approval followed in 1994 and since the UK Prospective Diabetes Study in 1997 (UKPDS) had clearly demonstrated the beneficial effects of metformin, it has been recommended as first-line treatment for type 2 diabetic patients (2).

### **Metformin mechanisms of action**

The classical antihyperglycemic function of metformin takes place at multiple sites of action in the body and through multiple molecular mechanisms that have been described in detail elsewhere (1,2). Briefly, its blood glucose-lowering ability is a combination of effects that metformin exerts in the liver, the gastrointestinal tract and in the muscles.

In the liver, gluconeogenesis is downregulated through both AMPK-dependent and -independent signaling pathways. The AMPK-pathway is the cellular energy sensor and regulator of the cell’s energy homeostasis. If the ratio of AMP:ATP increases, the AMPK-pathway induces a switch from ATP-consuming pathways to ATP-generating pathways. This includes downregulation of gluconeogenesis and hence, a reduction of glucose levels (1,2).

In the gastrointestinal tract, metformin is thought to increase glucose uptake and metabolism by colonic enterocytes (1). Moreover, increased GLP-1 receptor secretion has been reported in response to metformin. Activation of the GLP-1 receptor results in increased insulin release (2). Finally, metformin seems to be related to shifts in the composition of the gut microbiome, but it remains unclear if and how changes of the gut microbiome lead to glucose-lowering effects (2). It is postulated that a healthier gut microbiome suppresses postprandial hyperglycemia and that levels of inflammatory cytokines are reduced (1).

In skeletal muscles, metformin has been reported to increase insulin-stimulated uptake of glucose. Newer investigations, however, indicate that this effect is of a more secondary nature by the metformin-induced overall improvement of glycemic control and reversal of glucose toxicity (2).

### **Metformin and AMD**

As described above, the pathophysiology of AMD primarily affects the interface of photoreceptors, RPE cells, the choroid and choriocapillaris. The association of metformin with AMD has been investigated in some preclinical trials, some retrospective trials and some systematic reviews and meta-analyses. We will summarize the results in the following sections.

### **Effects of metformin in preclinical trials**

The group of Ying et al. investigated the effects of metformin in a mouse model of laser-induced exudative AMD as well as in the human umbilical vein endothelial cell (HUVEC) line (28). Mice treated with metformin had significantly smaller CNV lesions with reduced vascular density than the control group. Their experiments with HUVEC cells showed that activin receptor-like kinase 1 (ALK1), a receptor which is essential for vascular development, remodeling and pathological angiogenesis, is inhibited by AMP-activated protein kinase (AMPK) and that metformin is a potent activator of AMPK (28).

Qu et al. examined the effect of metformin on the human retinal pigment epithelium cell line ARPE-19. Cells were put under oxidative stress via glyoxal-induced cytotoxicity (29). Metformin was able to protect ARPE-19 cells by inhibiting cell death, by reducing intracellular ROS production, by decreasing the apoptosis rate and by increasing intracellular NO levels, an important molecule for maintaining retinal homeostasis (29). A subset of experiments confirmed that metformin influences antioxidant and autophagy pathways to exert its function (29). Similar experiments have been performed by Zhao et al. using two different human pigment epithelium cell lines (30). Their experiments showed that H2O2-induced oxidative damage was attenuated by metformin. Metformin stimulated autophagy via the AMPK-pathway (30).

The *in-vivo* experiments performed by Xu et al. using different mouse models for retinal and photoreceptor degeneration corroborate the results of the above described *in-vitro* experiments (31). Xu et al. showed that metformin was able to protect the retina from degenerative oxidative stress-induced damage. The results indicate that metformin activates AMPK as the underlying mechanism of action (31).

The group of Han et al. elucidated the anti-angiogenic and anti-inflammatory effects of metformin in a set of *in-vitro* and *in-vivo* experiments (32). They found that metformin had significant anti-angiogenic effects by inhibiting proliferation, migration and tube formation of human retinal vascular endothelial cells. In addition, metformin had potent anti-inflammatory effects by suppressing several inflammatory cytokines through both AMPK-dependent and AMPK-independent pathways (32).

### **Effects of metformin use on AMD in retrospective clinical trials**

Several retrospective studies have analyzed the association of metformin use with AMD. Five studies exclusively determined the association of metformin use and the risk of developing AMD in diabetic patients (33–37), whereas three studies included broader patient groups according to their cohort definition (38–40). One study examined the association of metformin use with dry AMD only (33), while the remaining studies considered all forms of AMD or did not further specify.

Five out of eight retrospective studies found associations of metformin with decreased odds of developing AMD (35–39), one study found conflicting associations (33) and two studies report no association of metformin use with the development of AMD (34,40). Three studies found positive associations with either duration of metformin use or dose-dependent effects (35,37,38), while one study did not detect an association with longer metformin use (40).

Romdhoniyyah et al. performed a meta-analysis over five retrospective trials (3). They found a positive odds ratio for the association of metformin use and the risk to develop AMD but their analysis did not reach the level of significance.

### **Metformin and anti-VEGF therapy**

A prospective trial by Shao et al. found that metformin enhanced the effect of anti-VEGF therapy in patients with diabetic macular edema (DME) (41). The group taking metformin for 6 months or more had better BCVA and larger central macular thickness (CMT) reduction following anti-VEGF injections as compared to the group not taking metformin. In addition, the metformin group required less total number of injections over time. The authors postulate that the reported anti-angiogenic function together with its anti-inflammatory effects via regulation of the AMPK/mTOR signaling pathway could be responsible for the observed enhancement of anti-VEGF therapy (41).

### **Metformin and other diseases**

According to an increasing number of publications, metformin seems to exert beneficial functions for a variety of other diseases than AMD. It is not the scope of this review to cover all these diseases, but Lv and Guo have recently published a review summarizing diseases with potential benefits of metformin use (42). Briefly, in addition to diabetes and AMD, these include various forms of cancer (breast cancer, blood cancer, colorectal cancer, endometrial cancer, melanoma, bone cancer), obesity, liver diseases, cardiovascular diseases and kidney diseases. Last but not least, metformin is under discussion as an anti-aging therapy (42).

### **Proposed mechanisms of action**

The exact mechanisms of the multiple effects of metformin are still under investigation. However, some possible signaling pathways and/or modes of action have already been identified.

The AMPK-pathway appears to play a central role in the action of metformin. The AMPK-pathway is a central regulator of the cellular metabolism (43). AMPK becomes activated when the level of ATP decreases indicating high metabolic activity. Via direct phosphorylation of a number of proteins, AMPK downregulates energy-consuming pathways and promotes the activation of energy-producing pathways to restore energy homeostasis of the cell (43). In this way, the AMPK-pathway plays a major role in the regulation of glucose metabolism, lipid metabolism, cell growth and autophagy. As described earlier, AMD pathophysiology relies on the integrity of the RPE cells, which are the critical interface between photoreceptor cells and the choroid. Dysregulation of RPE metabolic pathways, especially of the AMPK/SIRT1/PGC-1a and of the mTOR pathway are strongly associated with AMD pathophysiology (44). Metformin directly influences the mitochondrial respiratory chain thereby inducing the AMP-mediated activation of AMPK, the initial step of the AMPK-pathway (2,7). Downstream-signaling within the AMPK pathway is complex. This could explain why the beneficial functions of metformin are as diverse as anti-inflammatory, anti-oxidative, anti-angiogenic and anti-apoptotic (45).

A second mode of action, is the ability of metformin to reduce chronic inflammation by improving the metabolic state. Additionally, several direct anti-inflammatory effects have been described, although not directly in the context of AMD but as a general effect of metformin (46). This includes decreasing reactive oxygen species and lowering levels of inflammatory cytokines (46). Interestingly, in the context of acute respiratory distressed syndrome (ARDS), a common inflammatory condition in severe Covid-19, metformin has been shown to inhibit the activation of the NLRP3 inflammasome thereby ameliorating the course of this life-threatening complication (47). This corroborates findings that another direct NLRP3 inhibitor (fluoxetine) is associated with reduced risk to develop AMD. Possibly, metformin is able to prevent NLRP3 inflammasome activation in RPE cells to prevent their degeneration (48).

# **CONCLUSION**

Evidence is increasing that metformin, the most commonly prescribed oral antihyperglycemic drug, influences a variety of physiological functions besides its classical glucose-lowering effect. Essentially, this includes anti-inflammatory, anti-angiogenic, anti-oxidative, anti-apoptotic, neuroprotective and anti-ageing effects. In addition, it has been shown that metformin is able to enhance the effect of anti-VEGF agents in the treatment of diabetic macular edema. The latter is especially interesting for patients with reduced anti-VEGF responses. Further investigations should elucidate the underlying mechanism of action and if this effect can also be observed in patients with neovascular AMD.

Beyond all the reported beneficial properties of metformin, there are also some disadvantages associated with the use of metformin that should be taken into account before using metformin as a "cure it all medication". Reported disadvantages include vitamin B12 deficiency, increased risk of lactic acidosis, and alteration of 745 proteins with uncertain consequences (7). On top of that, metformin is known to have various gastrointestinal side effects, although these can be minimized by gradually increasing the dose, for example.

Furthermore, a study of Ebeling et al. that analyzed the influence of metformin on individual patient-derived RPE cell-lines indicated that the effect of metformin was not uniform across all patients. The group suggests that patient specific responsiveness to metformin should be taken into account before prescription and that approaches towards personalized medicine are necessary (49).

In the future, more prospective trials are needed to confirm in more detail how the beneficial effects of metformin influence the pathophysiology of AMD and other diseases for which metformin use has been associated with beneficial outcomes. There is one ongoing prospective, phase II clinical trial that is investigating the ability of metformin to decrease the progression of geographic atrophy in non-diabetic patients with AMD (50). Study completion is expected by the end of 2024.

# Author’s contributions

The authors contributed equally to the article.

# Conflicts of interest

I declare that I have no conflicts of interest.

# Ethical approval and consent to participate

Not applicable.

# Consent for publication

Not applicable.

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