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THE EFFECT OF FENOFIBRATE ON THE DEVELOPMENT OF DIABETIC RETINOPATHY AND NEPHROPATHY – A REVIEW OF CURRENT RESEARCH

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ABSTRACT

The aim of this review is to summarize current knowledge on the effect of fenofibrate in reducing the risk and progression of two major diabetes complications: retinopathy and kidney disease. We also discuss the mechanisms underlying fenofibrate's potential protective effects and the pathophysiology of these complications.
A literature search was conducted in PubMed and Google Scholar, with emphasis on publications from 2020–2025. The search strategy included terms such as "fenofibrate diabetes," "fenofibrate nephropathy," "fenofibrate retinopathy," "diabetic kidney disease," and "diabetes dyslipidemia."
Diabetes mellitus affects over 537 million people worldwide, reducing quality of life and creating a major healthcare burden. Fenofibrate, a fibrate-class lipid-lowering agent, has gained attention due to its frequent use in patients with diabetes and dyslipidemia. Evidence suggests that fenofibrate may slow the progression of diabetic retinopathy, reducing the need for surgical interventions, and may also decrease albuminuria and delay the progression of diabetic kidney disease.
In conclusion, fenofibrate appears to have potential as an adjunct therapy for preventing microvascular complications of diabetes, although further research is required to confirm its long-term benefits.

KEYWORDS

Fenofibrate, Diabetes Mellitus, Retinopathy, Nephropathy, Diabetic Kidney Disease

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Fenofibrate and its action

Fenofibrate is a drug from the fibrate group, being a prodrug containing fenofibric acid combined with an isopropyl ester. It has lipid-lowering properties, therefore its main indications for treatment are: severe hypertriglyceridemia (regardless of the concentration of the HDL cholesterol fraction), mixed hyperlipidemia when the use of statins is not recommended or they are not tolerated and in the case of mixed hyperlipidemia, when the risk of cardiovascular diseases is high and the previous statin treatment does not allow for sufficient control of the level of triglycerides and the HDL cholesterol fraction as an addition to the previously used statins[1][2][4][5]. The lipid-lowering effect of fenofibrate is to reduce the concentration of triglycerides and the VLDL and LDL cholesterol fractions, and to increase the concentration of the HDL cholesterol fraction. From a biochemical point of view, it results from binding to and activating the nuclear receptor PPAR-α - this leads to increased synthesis of lipoprotein lipase, which in turn leads to increased catabolism of triglycerides; it also leads to a decrease in their synthesis by increasing the activity of enzymes of β-oxidation of fatty acids. The effect on the level of cholesterol fractions results from increased synthesis of the HDL fraction (due to increased production of apolipoproteins AI and AII) and due to the production of VLDL and LDL of normal size and composition (due to reduced production of apolipoprotein AIII) [6] [7]. It also has properties that increase the reverse transport of cholesterol from tissues to the liver, which allows slowing down the progression of atherosclerosis in blood vessels. An important feature of fenofibrate is also its anti-inflammatory effect - studies have shown its effect on the modulation of inflammatory pathways by activating the PPAR-α receptor and reducing the production of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) and increasing the production of anti-inflammatory cytokines such as IL-10[3][7].

Diabetes - characteristics of the disease

Diabetes is a group of metabolic disorders characterized by elevated blood glucose levels (hyperglycemia), which occur through various mechanisms. Typical symptoms of diabetes include: fatigue and drowsiness, polydipsia and polyuria, polyphagia, and weight loss. The intensity of these symptoms may vary depending on the stage of the disease[8][9].

The most common types include type 1 diabetes (resulting from dysfunction of the cells of the islets of Langerhans, which leads to insufficient production of insulin by the pancreas and, as a consequence, to its cessation) and type 2 diabetes (resulting primarily from resistance of the body's cells to insulin, which in turn causes the production of excessive amounts of insulin, then in amounts exceeding the production capacity of the pancreas and its endogenous insufficiency) [8][9][10]. In the long term, the hyperglycemic state leads to negative micro- and macroangiopathic changes, which in turn lead to the development of chronic changes in, among others, the eyes, kidneys, nervous system, circulatory system, heart and other complications resulting from hypoperfusion of the body's peripheral tissues [9][10].

The main factor and symptom taken into account when diagnosing type 2 diabetes is the measurement of the glycemia level. When measuring fasting - the normal blood sugar level is considered to be 70-99 mg/dl, the abnormal fasting glycemia is considered to be 100-125 mg/dl, and with a double measurement >= 126 mg/dl we can talk about the diagnosis of diabetes. The diagnosis can also be made using an oral glucose tolerance test (OGTT) - blood is taken for testing from the patient, who then consumes a solution containing 75 g of glucose in a short time interval, and then after 120 minutes the glycemia is measured again. If after 2 hours the glycemia is 140-199 mg/dl we can confirm the abnormal glucose tolerance; with a result >= 200 we can make the diagnosis of diabetes. In the case of blood glucose measurement at any time of the day, the diagnosis can be made after obtaining a blood glucose level of >=200 mg/dl with the simultaneous presence of symptoms typical of diabetes (polydipsia, polyuria)[8].

Due to the significant impact of hyperglycemia as a factor that has the greatest impact on the risk of developing and progressing diabetes complications, the treatment of this disease is based in the initial stage on lifestyle changes, implementing a low-glycemic diet and trying to eliminate other environmental factors, and if the previous ones are ineffective, on implementing oral pharmacotherapy with hypoglycemic drugs. These drugs differ in the mechanism by which they affect glycemia levels - they can inhibit the release of glucose from the liver (metformin) or from complex carbohydrates absorbed in the intestine (alpha-glucosidase inhibitors), increase insulin secretion by the pancreas (sulfonylureas, meglitinides), and reduce tissue resistance to insulin (PPAR agonists). In the case of type 1 diabetes and late stages of type 2 diabetes, exogenous insulin and its analogues are also used in the treatment.[9][10]

Diabetes is one of the most serious challenges facing healthcare systems in both developed and developing countries from an epidemiological perspective. Estimates of the number of people with diabetes in 2022 are around 828 million worldwide. There is an upward trend in the number of people with diabetes on all continents, especially in people with a lower socioeconomic position. The trend of increasing the incidence of type 2 diabetes in children, who were previously diagnosed with type 1 diabetes, is also becoming worrying. WHO estimates the annual number of deaths caused by diabetes at around 1.5 million, and even 4.2 million if its complications are taken into account. [11]

Uncontrolled and chronic hyperglycemia significantly affects small blood vessels, which has a major impact on the mechanism of later diabetes complications. It leads to the reaction of glucose molecules with proteins that build vessel walls, which leads to the formation of advanced glycation end products (AGEs), which reduce the elasticity of vessel walls and activate RAGE receptors on vascular endothelial cells, which leads to increased local inflammation and oxidative stress, among others through the activation of the nuclear factor NF-κB, which in turn stimulates cells to produce pro-inflammatory factors such as TNF-α, IL-1, IL-6, chemokines and adhesion molecules (e.g. VCAM-1, ICAM-1) [12]. The increased production of free oxygen radicals is also not without influence - this is due to the activation of the above. RAGE receptors, by overloading mitochondrial respiratory chains (resulting in the formation of superoxide anions (O_2^-), as well as by damaging superoxide dismutase (SOD), i.e. one of the enzymes neutralizing O_2^-. Hyperglycemia also affects the increased synthesis of diacylglycerol, which in turn activates protein kinase C, which leads to increased vascular permeability, as well as to the stimulation of the production of compounds associated with angiogenesis (VEGF), which leads to the formation of new, abnormal blood vessels. Glycation of the eNOS enzyme leads to a disturbance in the synthesis of nitric oxide, which also has a negative effect on the ability of vasodilators and the regulation of blood flow[12].

Diabetic retinopathy - mechanism of development, treatment, epidemiology

Diabetic retinopathy is a chronic complication of diabetes resulting from damage to the blood vessels in the retina, the part of the eye that allows for the reception of visual stimuli. It manifests itself among others gradual deterioration of vision quality, appearance of floaters and other visual field disturbances, impaired vision in the dark and, in the long term, vision loss[13]. Factors influencing its development include uncontrolled blood pressure, hyperlipidemia and chronic and uncontrolled hyperglycemia. This complication develops against the background of damage to small arterioles of the eye and their closing, which impairs the perfusion of retinal cells. In a later stage, neovascularization occurs, also in the area of the optic nerve head. Due to their pathological origin, the newly formed vessels often rupture, which leads to the occurrence of small hemorrhages, also into the retina[15][22]. This complication can develop into maculopathy, when the macula, which has the largest number of cones, becomes swollen and damaged [13].

The most commonly used scale of progress of diabetic retinopathy is ICDR scale (International Clinical Diabetic Retinopathy Disease Severity Scale) is also used, taking into account the absence (without DME) or the presence of macular edema (DME) when a change in the macular area is observed causing retinal thickening and/or hard exudates[13].

Table 1. International Clinical Diabetic Retinopathy Disease Severity Scale

Retinopathy type:	Changes observed in the study that qualify for the qualification of a given type:
No signs of diabetic retinopathy	No irregularities
Mild diabetic retinopathy	Only microaneurysms (small bulges of retinal vessels)
Moderate diabetic retinopathy	Microaneurysms and other changes (e.g. hemorrhages, hard exudates) occurring to a lesser extent than in the severe form of retinopathy
Severe diabetic retinopathy	At least one of the following changes: - ≥20 hemorrhages in ≥4 quadrants - retinal varicosity in ≥2 quadrants - pronounced IRMA in ≥1 quadrant - without signs of proliferation
Proliferative retinopathy	Symptoms of severe retinopathy + at least one of the following symptoms: - Neovascularization - Preretinal hemorrhage - Vitreous hemorrhage

It is one of the most common complications of diabetes - after a period of the disease lasting at least 15 years, its traces are noticeable in almost all patients with type 1 diabetes and in over 60% of patients with type 2 diabetes.

Due to the common occurrence of retinopathy and its significant reduction in the quality of life of patients, regular eye check-ups are recommended for patients at risk. Patients with type 1 diabetes should have an eye test within 5 years of diagnosis and then annually. Patients with type 2 diabetes should have an eye test immediately after diagnosis and it should also be repeated annually. If a patient is diagnosed with diabetic retinopathy, more frequent check-ups are recommended - usually every 3-6 months, depending on the advancement of the changes. These tests are particularly important because the disease is often asymptomatic in its early stages[13].

The basis of diabetic retinopathy treatment is maintaining metabolic factors within the norm (maintaining glycated hemoglobin level <7%) and pharmacological control of blood pressure (use of ACEI, ARB) and lipidemia (therapy with statins, fibrates). In the case of more advanced changes, invasive methods are used, such as laser photocoagulation, intravitreal injections with glucocorticosteroids or anti-VEGF drugs, and vitrectomy[13].

The use of fenofibrate and the impact on the development of diabetic retinopathy

Fenofibrate slows down its progression through several mechanisms of action, confirmed in large clinical studies. Thanks to its effect on the modulation of inflammatory pathways, reduction of cytokine and angiogenic compounds production and reduction of oxidative stress, it limits inflammatory processes and oxidative damage, which have a major impact on the genesis of retinal and macular damage. It also allows to limit the permeability of retinal vessels, which leads to reduced vascular leakage and the formation of macular edema. Thanks to this, the blood-retina barrier remains tighter, which prevents the penetration of harmful substances and inflammatory cells into the retina[15]. Its effect on protection against hyperlipidemia and hypertriglyceridemia, which are harmful to the microcirculation in the retina, has also been confirmed[14].

A particular impact was noted in patients who already had early-onset retinal changes. A 2021 clinical trial showed a reduction in the progression of retinopathy to an advanced stage or requiring invasive therapy (intravitreal injections, laser therapy, vitrectomy) - 22.7% in patients treated with fibrate vs 29.2% in untreated patients after 4 years[19].

Other studies have also confirmed the effect of fenofibrate therapy on a significant decrease in the progression of changes. Analyses have shownamong othersa decrease in the progression of non-proliferative retinopathy to life-threatening diabetic retinopathy by 8%) and a decrease in the need for retinal laser therapy by 30% after a year of treatment and by 23% during the entire treatment period[16][19]. Some studies also address the issue of fenofibrate from the level of lipidemia control, such as the 2020 study, which examined the effect of statin and fenofibrate therapy on the development of diabetic retinopathy - a significant reduction in the risk of development was found in relation to statin therapy alone[20]. It is also worth mentioning the study that showed a positive effect of fenofibrate use on the number of hematopoietic cells circulating in the blood, which may have an impact on increased regeneration and a reduction in the risk of progression of microangiopathic disorders of the retina and macula[21]. Importantly, studies also indicate a possible increase in the risk of adverse effects in patients treated with fenofibrate - caution and individualization of treatment are indicated[30][31].

Diabetic Kidney Disease (DKD) - Mechanism of development, treatment and epidemiology

Diabetic kidney disease (formerly also called diabetic nephropathy) is a complication of diabetes with a non-inflammatory secondary glomerulopathy (glomerular disease) character, resulting from chronic hyperglycemia and microangiopathic changes resulting from it. Renal glomeruli, renal tubules, afferent and efferent renal arterioles are damaged. The destructive effect of high blood glucose levels on the formation of DKD results mainly from the proinflammatory effect - increased secretion of proinflammatory cytokines (TNF-α, IL-1, IL-6), chemokines, adhesion factors, free oxygen radicals and increased vascular permeability. As in diabetic retinopathy, advanced glycation end products (AGEs) have a major impact[18]

Diabetic kidney disease together with hypertension are the most common cause of end-stage renal failure in Poland (42%). Statistically, diabetic kidney disease itself affects approximately ⅓ of patients with type 1 and 2 diabetes. However, in recent decades, a decrease in the incidence of the disease has been observed in diabetics, probably due to the widespread use of effective insulin therapy and drugs inhibiting the RAA system[23].

The progression factors include:m.including uncontrolled hypertension (the single most important factor of progression), cigarette smoking, activation of the renin-angiotensin-aldosterone system, urinary tract infections, urinary obstruction, high-protein and high-sodium diet, male gender, older age and genetic factors (particularly important in the prognosis of advanced forms of DKD)[18].

From a pathophysiological point of view, the earliest stage of the disease is an increase in renal filtration (GFR up to 160 ml/min) resulting from the osmotic effect of glucose and an increase in intraglomerular pressure. This leads to the progression of the renal hypertrophy process and the initiation of a whole series of histological changes - changes in the basement membrane of the glomerulus, damage to podocytes, proliferation of mesangial cells, its proliferation and penetration into the capillaries (the so-called Kimmelstiel-Wilson nodules are formed). After the period of initial hyperfiltration, there is a period of clinically silent deterioration of the excretory functions of the kidneys due to progressive processes and histological changes. The period of progression to the appearance of the first clinical symptoms is about 5-10 years. Such a period is usually albuminuria - initially the values of excreted protein oscillate around 30-300 mg albumin/24h. There is also a decrease in GFR and an increase in blood pressure. Lack of intervention leads to the development of constant proteinuria (>300 mg of excreted albumin/24h). Further decrease in renal filtration function, increase in blood pressure and occurrence of lipid disorders occur. In this period, peripheral tissue edema also appears resulting from the loss of albumin with urine. Further development leads to the occurrence of end-stage renal failure and the need for renal replacement therapy[18][24]

From the patient's perspective, the first symptom noticed is often nocturia (the need to urinate at night), frequent urge to urinate during the day, and later on, edema, nausea and vomiting (resulting from impaired urea excretion mechanism). With progression, insulin metabolism in the kidneys decreases - more frequent episodes of hypoglycemia in patients treated with insulin may indicate a decrease in kidney function[18]

Screening tests in patients with diabetes are performed in two ways - measurement of albumin excretion in urine (determined based on 24-hour urine collection or albumin-creatinine ratio (ACR)) or measurement of serum creatinine concentration. Based on creatininemia, glomerular filtration rate (GFR) can be determined - in the case of diagnosing diabetic kidney disease, the MDRD formula seems to be more accurate than the Cockroft-Gault formula. The condition for diagnosing DKD in a patient with diabetes is the finding of albuminuria >30 mg/g and/or reduced GFR, after excluding other possible causes of chronic kidney disease.[18][24]

Due to the initially clinically silent (lack of albuminuria) course of DKD, the first tests in patients with type 1 diabetes are usually performed about 5 years after diagnosis. Patients with type 2 diabetes are usually diagnosed after a longer period of its duration, therefore the first tests are performed at the diagnosis. Regardless of the type of diabetes, it is recommended to perform annual check-ups - both measurement of albuminuria and serum creatinine and determination of GFR. In case of doubts as to the background of albuminuria and filtration disorders, a kidney biopsy is performed - however, due to the invasive nature of the test and possible complications, it is not performed often[24].

Treatment of DKD mainly involves:

- Glycemic control - important due to the negative impact of chronic hyperglycemia on many other systems (visual organs, nervous system). The greatest benefits in reducing the progression of DKD are achieved at a glycated hemoglobin concentration of around 7%
- Blood pressure control - this is the single most important factor in the progression of DKD - in diabetic patients, more intensive reduction of blood pressure values effectively reduces the risk of disease progression. Of particular importance in this regard is the influence of blood pressure lowering drugs (ACEI, ARB), which by inhibiting the RAA system have a beneficial effect on reducing the risk of progression.[24]
- Control of cardiovascular risk and lipidemia
- Controlling the supply of protein and sodium in the diet

Fenofibrate use and impact on development of diabetic kidney disease

Several studies have shown the actual effect of fenofibrate on reducing the progression of diabetic kidney disease. A particularly large effect was observed in the reduction of urinary albumin excretion[25]. The drug's action in this regard is based on several mechanisms. Firstly, the effect of fenofibrate as an anti-inflammatory agent is important here due to its effect on the decrease in the production of pro-inflammatory cytokines, chemokines and adhesion factors. Its effect on reducing oxidative stress and reducing the number of free radicals is also important here[27]. It is worth remembering its role in maintaining a proper lipid profile, because as proven in studies - lipidemia control is one of the key elements of DKD treatment. However, it should be remembered that studies have shown that fenofibrate exerts its nephroprotective effect even without the lipid-lowering effect[17]. Some studies have also noted the benefits of concomitant therapy with fenofibrate and drugs that inhibit the renin-angiotensin-aldosterone system (ACEI or ARB) in terms of enhancing their nephroprotective effect, especially in diabetic patients with concomitant diabetic retinopathy.

In the context of fenofibrate therapy in patients with diabetic kidney disease, the issue of safety should also be mentioned. Fenofibrate is contraindicated in patients with severe renal impairment, while in patients with mild and moderate impairment, dose adjustments should be considered according to the patient's GFR results[28]. There are reports indicating the possibility of creatinine in patients treated with fenofibrate alone or in combination with statins, with these levels being stable during treatment and resolving after its discontinuation[29]. It is also worth remembering the risk of rhabdomyolysis - although it is mainly associated as an adverse effect during combined therapy with fibrates and statins, cases of rhabdomyolysis with fenofibrate monotherapy have also been described[30]. In view of this information, it is important to take into account the individual condition of each patient during therapy and to adjust the therapy adequately to their situation, while maintaining safety and monitoring renal parameters, which should be the basis in patients treated for DKD[26].

Discussion and conclusion

Due to the ever-increasing number of diabetics and the increasing impact of this disease on the burden on the healthcare system and the decline in the quality of life of patients, ways are still being sought to reduce the risk of chronic complications of diabetes affecting various body systems. Fenofibrate appears to be one of such factors, especially due to its main, hypolipidemic effect, useful in diabetics, often struggling with dyslipidemia. It also demonstrates significant anti-inflammatory and antioxidant effects, important in the context of the microangiopathic background of some chronic complications of diabetes, such as diabetic retinopathy or diabetic kidney disease. Especially in the case of these diseases, the reduction of progression is visible. Fenofibrate allows for the reduction of the progression of diabetic retinopathy and a reduction in the group of patients who would need laser therapy or other invasive treatment. Similarly, in the case of diabetic kidney disease, a decrease in albuminuria, which is one of the main indicators of disease progression, and a slowdown in the decline of GFR are observed in the case of fenofibrate therapy. At the same time, attention is drawn to the need to individualize treatment and monitor the safety of therapy due to the possibility of adverse effects.

In summary, fenofibrate appears to be a valuable element of therapy in patients with diabetes and coexisting dyslipidemia, which may significantly reduce the risk of progression of serious chronic complications of diabetes, such as diabetic retinopathy or diabetic kidney disease.

Author's contribution

Conceptualization, Kacper Szeląg and Piotr Świerczek; methodology, Karolina Błądzińska; check, Małgorzata Zach, Paula Folta and Cezary Lubas; formal analysis, Antoni Kujawski; investigation, Antoni Kujawski; resources, Piotr Świerczek; data curation, Joanna Kłosowska; writing - rough preparation, Kacper Szeląg; writing - review and editing, Małgorzata Zach; visualization, Anna Opalińska; supervision, Kacper Szeląg; project administration, Maciej Błądziński;

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