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Significance of dyslipidemia for primary open-angle glaucoma

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Reduction of intraocular pressure is currently considered as the main strategy to stop or slow down the progression of glaucomatous optic neuropathy. However, this goal is achieved in only 1 in 7 patients with primary open-angle glaucoma (POAG). Therefore, it is important to determine further risk factors that can be therapeutically influenced. One example of such risk factors is lipid metabolism disorders. ***Material and methods.*** *Literature search in PubMed using the queries "primary open-angle glaucoma" and "dyslipidemia" limiting oneself to the period from 2000 to 2021.* ***Results.*** *POAG is currently considered to be a systemic neurodegeneration with neuroinflammation at the forefront. Oxidized low density lipoprotein (oxLDL) acts as a free radical (so-called bioactive lipid) with pro-inflammatory properties and promotes glaucomatous neuroinflammation.* ***Conclusion.*** *In addition to a personalized targeted pressure-oriented intraocular pressure reduction, LDL-associated lipid metabolic disorders should be corrected in every POAG patient. LDL cholesterol below 100 mg/dl (2.6 mmol/l) in the blood is the critical threshold level.*

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Значение дислипидемии при первичной открытоугольной глаукоме

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Снижение внутриглазного давления (ВГД) в настоящее время считается основной стратегией остановки или торможения прогрессирования глаукомной нейропатии зрительного нерва. Однако эта цель достигается лишь у 1 из 7 больных первичной открытоугольной глаукомой (ПОУГ). В связи с этим важно определить дополнительные факторы риска, на которые можно воздействовать терапевтически. Одним из таких факторов риска может быть нарушение липидного обмена. ***Материал и методы.*** *Поиск литературы в PubMed по запросам «первичная открытоугольная глаукома», «дислипидемия» в период с 2000 по 2021 г.* ***Результаты.*** *ПОУГ в настоящее время считается системной нейродегенерацией с нейровоспалением как ключевым фактором. Окисленный липопротеин низкой плотности (ЛПНП) действует как свободный радикал (так называемый биоактивный липид) с провоспалительными свойствами, который способствует глаукоматозному нейровоспалению.* ***Заключение.*** *Помимо целевого персонифицированного снижения ВГД, у каждого пациента с ПОУГ следует скорректировать нарушения липидного обмена, связанные с ЛПНП. Пороговым ориентиром следует считать уровень холестерина ЛПНП в крови ниже 100 мг/дл (2,6 ммоль/л).*

Ключевые слова: глаукома; дислипидемия; митохондриальная патология; нейровоспаление

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In the treatment of glaucoma, the emphasis in daily practice is on achieving the target pressure, the individually targeted eye pressure level at which glaucomatous progression should stop as best it can, or progress only slightly. This therapy concept has been implemented for more than 100 years, but this therapy strategy shows only a very limited success. For example, 7 patients have to be treated with POAG to stop the progression in one patient (number needed to treat = NNT = 7) [1]. This is even more evident in patients with ocular hypertension (OHT). Here, the NNT = 16–20 [1, 2]. This means that 16–20 patients with OHT have to be treated to prevent conversion to POAG in 1 patient (!). In addition, the Early Manifest Glaucoma Trial showed that after 8 years of therapy with a mean achieved pressure of 15.5 mm Hg in newly detected glaucoma patients, progression was still 59% and differed only by 17% from the comparison group of glaucoma patients who received no therapy (79%) [3].

These results are quite sobering and demonstrate that the mere reduction of intraocular pressure alone is not sufficient to treat patients with POAG effectively. Therefore, it is absolutely time to reconsider the current therapy concept from both the clinical and the scientific point of view. This is not to question ocular pressure reduction per se as a reasonable way in a complex treatment strategy, but ocular pressure reduction must not remain the only treatment strategy. Our knowledge of POAG has improved considerably over the last 20 years, and yet this knowledge is rarely applied in practical glaucoma treatment. It is undisputed that POAG is a neuroinflammatory disease leading to cerebral neurodegeneration [4, 5]. The driving forces for this are primary mitochondrial dysfunction, primary vascular dysfunction, and immunologic dysregulation with the presence of various autoantibodies [6], which act both on the eye itself but, more importantly, systemically. These complex pathophysiological processes cannot be compensated by a local reduction of intraocular pressure. Therefore, we need a personalized holistic therapy strategy for each individual POAG patient in order to offer a meaningful therapy strategy according to his personal risk profile.

The main unifying therapeutic goal is to reduce the increased oxidative stress and with it the neuroinflammation. It is often overlooked that even the smallest step in this direction is an important component in the overall therapy concept. Even though randomized, prospective multicenter studies would certainly be useful to substantiate these approaches, we will still have to wait decades for this. However, the current knowledge already allows taking care of the containment of the increased oxidative stress now.

A complementary basis for a systemic view of POAG is the presence of systemic underlying diseases in addition to its own specific neuroinflammation. Arterial hypertension is present in about 50% and diabetes mellitus and dyslipidemia in 20–30% [7, 8]. However, these three systemic diseases themselves lead to an increased oxidative stress [9–11], whereby they additionally burden the glaucomatous neuroinflammation, in which they are also associated with a neuroinflammation [12]. Thus, it is part of the overall therapeutic concept of a POAG to also take care of the optimal adjustment of these underlying diseases [13].

The example of dyslipidemia will be used to illustrate this. During fat intake (triglycerides, cholesterol), fats are metabolized by the liver, released as very low density lipoprotein (VLDL) and later converted into LDL (low density lipoprotein). LDL thus transports cholesterol formed by the body itself from the liver to the tissues. It circulates in the blood for about five days and has a lipid content of about 80%. Under conditions of increased oxidative stress, LDL undergoes oxidation and becomes oxidated LDL (oxLDL) [14], which itself acts as a free radical as a so-called bioactive lipid with proinflammatory properties. The outer shell of oxLDL is altered in such a way that it no longer enters the cell via the LDL receptors and remains in the blood. It is highly immunogenic, leading to upregulation of scavenger receptors and toll-like receptors, activating adhesion molecules in endothelial cells [15], and promoting the conversion of monocytes to macrophages, which, however, cannot degrade oxLDL, leading to the formation of the characteristic foam cells in atherosclerotic lesions [14, 15]. Highly elevated oxLDL levels also result in increased free radical release in mitochondria [16], creating a self-sustaining cycle with chronic increase in oxidative stress.

In the context of primary mitochondriopathy in POAG, there is a generally increased cellular oxidative stress, so that this already sets the stage for oxidation of LDL to oxLDL. In human trabecular cells, the corresponding LDL receptors have been detected [17], the activation of which can lead to oxidative trabecular remodeling processes. OxLDL can stimulate the transcription factor NF-kB [18] and thereby release growth factors, such as TGF-β [19], which itself has an unfavorable effect on trabecular meshwork [20]. All together, oxLDL may unfavorably influence outflow resistance and increase intraocular pressure and/or limit the efficacy of local therapy.

In a recently published meta-analysis, increased triglyceride levels were detected in POAG patients [21] and in another meta-analysis a positive correlation between triglycerides and increased intraocular pressure was found [22].

What are the therapeutic consequences?

The most important basis is a differentiated blood lipid determination to detect dyslipidemia with elevated LDL levels. This should generally be done in case of a newly detected POAG and in the context of glaucomatous progression. Because patients with POAG can be classified as having moderate vascular risk, the target LDL level for this patient group is less than 100 mg/dl (2.6 mmol/L) according to the recommendations of the European Society of Cardiology [23]. For higher LDL levels, lifestyle changes are a good first therapeutic step, such as abstaining from nicotine, limiting the amount of coffee, eating a balanced diet, exercising, and avoiding pronounced stress situations for a longer period of time. However, these measures are only implemented by patients to a very limited extent [24]. Statins [25], which interrupt intracellular cholesterol formation, are therefore considered the therapy of choice. This results in increased expression of LDL receptors at the cell surface and increased reabsorption of LDL from the blood. Overall, the therapy is considered safe and effective, with myalgias and rarely glucose intolerance occurring in 0.1% as side effects, and the discussed risk of diabetes is considered low [26]. In patients with hyperlipidemia, after 2 years of statin therapy, the relative risk of POAG decreased by 8% and progression in glaucoma patients by 9% compared with those without statin therapy [27]. Supportively, data from the Erlanger Glaukom Register showed that progression of POAG as well as conversion of OHT to POAG is significantly reduced under statins [28].

In particular, the pleiotropic effects of statins have been shown to play an important role. Pleiotropic effects are therapeutic effects that are not related to the original main effect. For statins, mainly anti-inflammatory, immunomodulatory, and vascular endothelium-protective effects [25, 29], as well as neuroprotective effects [30–32] have been demonstrated, which can also meaningfully intervene in the disease process in POAG. Experimentally, neuroprotective effects have been demonstrated in an OHT animal model [33].

In addition, in the presence of dyslipidemia, local eye pressure-lowering therapy with β-blockers should be avoided because they, especially timolol, can increase triglycerides [34] and lower HDL cholesterol [34, 35].

In conclusion, dyslipidemia, specifically high plasma LDL, may intensify the neuroinflammatory events in POAG patients in which it negatively affects neurodegeneration such as in Alzheimer's disease [36, 37]. Therefore, in newly discovered POAG patients as well as in glaucomatous progression, blood lipids and especially LDL cholesterol should be determined in order to reduce them to below 100 mg/dl (2.6 mmol/l). In local therapy, β-blockers should be avoided.

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