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Clinical Metabolomics and Glaucoma

João Barbosa-Breda Uwe Himmelreich Bart Ghesquière
Amândio Rocha-Sousa Ingeborg Stalmans

Laboratory of Ophthalmology, Department of Neurosciences, KU Leuven, Leuven, Belgium

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Abstract
Glaucoma is one of the leading causes of irreversible blindness worldwide. However, there are no biomarkers that accurately help clinicians perform an early diagnosis or detect patients with a high risk of progression. Metabolomics is the study of all metabolites in an organism, and it has the potential to provide a biomarker. This review summarizes the findings of metabolomics in glaucoma patients and explains why this field is promising for new research. We identified published studies that focused on metabolomics and ophthalmology. After providing an overview of metabolomics in ophthalmology, we focused on human glaucoma studies. Five studies have been conducted in glaucoma patients and all compared patients to healthy controls. Using mass spectrometry, significant differences were found in blood plasma in the metabolic pathways that involve palmitoylcarnitine, sphingolipids, vitamin D-related compounds, and steroid precursors. For nuclear magnetic resonance spectroscopy, a high glutamine-glutamate/creatine ratio was found in the vitreous and lateral geniculate body; no differences were detected in the optic radiations, and a lower N-acetylaspartate/choline ratio was observed in the geniculocalcarine and striate areas. Metabolomics can move glaucoma care towards a personalized approach and provide new knowledge concerning the pathophysiology of glaucoma, which can lead to new therapeutic options.

Metabolomics

Metabolomics is the scientific study of the metabolic fingerprints that all cellular processes leave behind in a biological sample [1]. It provides a global perspective of all biochemical processes occurring in an organism at a certain time. Conversely, metabonomics, as it was first named by Jeremy Nicholson, refers to "the quantitative measurement of the dynamic multiparametric metabolic response of living systems to pathophysiological stimuli or genetic modification" [2, 3]. Metabolomics is the most recent of the "omics" fields, and it differs from other omics technologies because it considers the dynamic status of the human body. However, the concept behind the field can be traced back to the beginning of the last century, when physicians already understood the value of metabolites in the study of diseases [4]. The amount of knowledge gathered is rapidly growing, and in recent years the research subject has begun to change from in vitro and animal models to in vivo and human samples,

E-Mail karger@karger.com
www.karger.com/ore

João Barbosa-Breda
Laboratory of Ophthalmology, Herestraat 49
BE–3000 Leuven (Belgium)
E-Mail joao_breda@hotmail.com

which brings this technology closer to the patients' "bedsides" and enhances its clinical relevance. This research field can provide biomarkers and lead to a better understanding of the pathophysiologies underlying several diseases. The identified metabolites and metabolic pathways are closer to the phenotype than many other omics technologies; therefore, they are more easily translatable to clinical practice [5]. The metabolome is the sum of all metabolites in an organism, the result of internal processes (gene expression, protein activity, and cell metabolism) and the interaction between an organism and "external" factors (e.g., diet, health status, lifestyle, gut microbiome, drugs) [6, 7]. Metabolomics can be studied in organisms/whole organs, tissues, and fluids, in vitro and in vivo, either directly at eye level or systemically. The 2 main technologies currently used for these studies are mass spectrometry, which is more sensitive and can cover a wider range of metabolites but destroys the analyzed sample, and nuclear magnetic resonance (NMR) spectroscopy, which primarily detects soluble metabolites, does not destroy the sample, and can analyze in vivo samples noninvasively and repeatedly over time [8, 9]. Both technologies can simultaneously quantify a large number (hundreds to thousands) of metabolites, in a nontargeted approach, which has been defined as metabolic phenotyping or "metabotyping" [7].

Metabolomics in Ophthalmology

In ophthalmology, metabolomics has been used to study various eye diseases including glaucoma [10–16], age-related macular degeneration [17–19], diabetic retinopathy [20–22], keratoconus [23], refractive error [24, 25], retinal detachment [26], uveitis [27, 28], dry eye [29, 30], and other ocular surface diseases [31]. Analyses have been performed on tear fluid [23, 29–32], aqueous humor [24, 25, 33, 34], vitreous humor [20, 26, 27, 35, 36], cornea [37–39], conjunctiva [40], and lens [41, 42] samples.

This review aims to explain the importance of metabolomics in glaucoma and to summarize the findings of human studies.

Metabolomics in Glaucoma

Glaucoma is one of the leading causes of irreversible blindness worldwide [43], and the number of patients is expected to increase due to the aging population [44]. However, fast and reliable diagnostic methods are lacking. Indeed, clinicians rely substantially on regular structural and functional examinations until irreversible damage is detected. Moreover, substantial heterogeneity exists among patients. The incidence differs considerably between races, and the clinical manifestation and progression profiles are variable [11]. Genetic mutations and common genetic variants have been linked to several types of glaucoma, but these factors can only explain a small portion of all cases [45].

After establishing the diagnosis, clinicians face considerable uncertainty during the follow-up. The individual rate of progression varies considerably between patients, and it is impossible to know which patients will progress faster; therefore, intensive follow-up is advised (according to glaucoma management guidelines) until the rate is known [46–50]. To avoid an unacceptable burden on future health resources, it is important to better stratify patients according to their risk profiles. This process would allow more resources to be allocated to patients who are at higher risk of blindness (and avoid wasting resources on patients who do not need them) [51, 52]. Metabolomics has the potential to identify biomarkers that can be used for glaucoma diagnosis and prognosis. These results would allow for earlier diagnoses, when more visual function can be spared and less money spent on surgeries and frequent consultations, and, concurrently, help to better allocate the finite resources we have for high-risk patients.

The correlation between metabolomics and disease progression has not been studied, thus far, for any ophthalmological disease. However, a correlation with disease stage has been shown for diabetic retinopathy [21], as well as age-related macular degeneration [18, 19]. Similar studies have been conducted in cancer research, one of the largest areas of metabolomics research; preserved blood and urine samples have been used to metabotype progressive and/or relapsing patients. Some of these studies have focused on blood samples collected longitudinally to obtain data from different disease statuses for each patient [53]. However, glaucoma is a progressive chronic disease that does not have acute stages or recurrence/remission, and perhaps the best approach to understand what drives its progression is to collect either samples from patients with different rates of progression (case-control) or samples from a cohort and later analyze them according to progression outcomes (cohort) instead of longitudinal series of samples. A recent example of this one-time sample collection approach is a study of chronic lymphocytic leukemia patients (case-control) in which the authors sought to identify prognostic markers

Table 1. Metabolomics in glaucoma patients

Sample type	Altered metabolites/metabolic pathways
Mass spectrometry	
Blood plasma	Metabolic pathways involve palmitoylcarnitine, sphingolipids, vitamin D-related compounds, and steroid precursors [11]
NMR spectroscopy	
Vitreous	Higher Glx/Cr ratio [10]
LGB	Higher Glx/Cr ratio [10]
Optic radiation	No differences [16]
Striate area/ occipital cortex	Lower NAA/Cr and Cho/Cr ratios [14] No differences [13]

All studies compared glaucoma patients to healthy controls. NMR, nuclear magnetic resonance; LGB, lateral geniculate body; Glx, glutamine and glutamate; Cr, creatine/phosphocreatine; NAA, N-acetylaspartate; Cho, choline/phosphocholine/glycerophosphocholine.

of clinical aggressiveness at the time of diagnosis, which would direct treatment needs because current disease staging systems (Rai and Binet) are unable to discriminate between the stable and progressive forms of the disease in the early stages [54]. The Framingham Heart Study is an example of a metabolomics cohort study, in which baseline samples were used to predict clinical outcomes (diabetes incidence over a 12-year period [55], as well as the risk of metabolic syndrome after 5–7 years of follow-up [56]).

Apart from enabling the detection of different progression statuses, further knowledge regarding the pathophysiology of glaucoma can potentially create new drug development research lines, thereby expanding the potential therapeutic targets that we currently have available. Today, the mainstay of treatment relies on lowering intraocular pressure, either with medical or with surgical treatment. Although intraocular pressure is the primary risk factor, some patients present with glaucomatous neuropathy and progress towards blindness with lower-than-normal intraocular pressure values. Thus, we can conclude that other mechanisms exist for retinal ganglion cell death. A reduction or dysregulation of blood supply to the optic nerve is one potential mechanism in which local and/or systemic conditions, such as systemic hypotension [57–59], would favor an ischemic insult of the optic nerve [60]. Other potential damage pathways are increased apoptosis (increased neurotoxicity, neurotrophin depletion) and oxidative stress, among others. Several oxidative stress markers have already been shown to exist in the blood and aqueous humor of glaucoma patients (malonyldialdehyde was found to be the best serum biomarker) compared to controls [61–64]. Hence, we can conclude that glaucoma is a multifactorial disease.

In addition to local factors, systemic conditions have been shown to influence glaucoma pathogenesis. Therefore, metabolomics of ocular and systemic samples will potentially contribute to a better understanding and early diagnosis of glaucoma (Table 1). Indeed, a blood-plasma comparison between primary open-angle glaucoma patients and healthy controls using mass spectrometry found significant differences in specific metabolic processes involving palmitoylcarnitine, sphingolipids, vitamin D-related compounds, and steroid precursors. These observations might be linked to mitochondrial dysfunction and energy metabolism changes [11]. This study was the first attempt to perform a metabolome-wide analysis of glaucoma patients. Future studies can focus on certain glaucoma endotypes and investigate other sample types, such as aqueous humor or vitreous. In addition, excluding prevalent systemic diseases that can considerably alter metabolism, such as diabetes, might allow for a more accurate identification of glaucoma biomarkers.

In terms of NMR spectroscopy, several in vivo studies have been performed to assess the brain metabolite changes in glaucoma patients. Using localized, single-voxel in vivo NMR spectroscopy, no significant changes were found in the concentrations of typical metabolites N-acetylaspartate (NAA), creatine/phosphocreatine (Cr), and choline/phosphocholine/glycerophosphocholine (Cho) in the striate area compared to healthy controls [13]. However, the authors explained that this result might have been due to the slowly progressive nature of the disease because a substantial proportion of the decrease in the neuronal marker NAA occurs in the acute phase of cell degeneration. Another possible explanation is that the affected region might have been too small to allow for proper measurement, requiring more advanced NMR spectroscopic approaches. Later, a study performed with multiple-voxel NMR spectroscopy found lower NAA/Cr and Cho/Cr ratios in the geniculocalcarine and striate areas of glaucoma patients when comparing them to age- and gender-matched healthy controls [14]. A similar study was conducted in a rat model of ocular hypertension, and a lower Cho/Cr ratio was also found in the visual cortex 6 weeks after the start of ocular hypertension. However, no significant differences were found in other metabolites, including NAA, glutamine, and glutamate [15]. These changes could point towards a patho-

physiological mechanism of glaucoma involving a dysfunction of the cholinergic system. Hence, the Cho/Cr ratio could potentially serve as a noninvasive biomarker.

The vitreous has also been studied in human patients. In view of the apoptosis theory, in which the neurotoxicity of glutamate plays a pivotal role, a study was conducted with in vivo single-voxel NMR spectroscopy of the vitreous and lateral geniculate body of glaucoma patients. The authors found a higher glutamine-glutamate/Cr ratio in the vitreous and in the lateral geniculate body compared to healthy controls [10]. All of the study subjects were Caucasian, and hypertension, diabetes, and degenerative central nervous system diseases were excluded. No significant changes were found in the NAA/Cr and Cho/Cr ratios in the lateral geniculate body. These findings support the apoptosis theory, in which glutamate is one of the main contributing factors to neurotoxicity. Similar changes have been found when using high-pressure liquid chromatography to analyze vitreous samples of glaucoma patients [65]. Another study with the same technique showed no changes in glutamate in vitreous samples from glaucoma patients [66]. However, this result might have been due to the small sample size (8 glaucoma patients) and the heterogeneous sample (Axenfeld-Rieger and uveitis were also included) in the latter.

Recently, the metabolic pattern of optic radiations was compared between glaucoma patients and healthy controls, using a single-voxel NMR spectroscopy approach. The authors investigated the metabolite changes according to disease severity. No significant differences were found between groups or between disease severity levels. This result might have been due to a different site chosen for the measurement, a different (single- vs. multiple-voxel) technique applied, and/or significant age differences between the groups [16].

Pitfalls of Metabolomic Studies

In metabolomic studies, it is important to prevent and correct for sources of bias, such as age and gender, diet and lifestyle, the time of day of sample collection, and temperature and time to storage. In addition, systemic diseases and intake of drugs and supplements can potentially alter the metabolome and should be accounted for. Despite this, some studies have already been conducted with previously preserved samples (5–9 years) collected and handled under suboptimal conditions. For instance, one study investigated blood and urine metabolic differences in patients with multiple myeloma. Samples were collected at different times of the day, with no fasting, and they were delivered by post, thus spending 1–3 days at ambient temperature. Even under such conditions, significant differences were found between newly diagnosed myeloma requiring therapy, remission after treatment, and relapse patient groups. Bias sources were clearly present, and the findings should be viewed under that consideration, but the findings still support researchers who argue that standardization of procedures is more important than the best collection and handling conditions [67].

Data analysis and statistics are also important. Although the number of metabolomics libraries and the amount of knowledge increase every day, there are still several peaks in spectra that cannot be linked to known metabolites or metabolic pathways. In addition, there are many detectable metabolites; therefore, a proper statistical analysis must be performed to account for multiple comparisons and a high level of false positives (e.g., Benjamini-Hochberg false discovery rate-controlling procedure) [2, 5, 6, 68–72]. Due to the large number of detectable metabolites, in particular in the spectra of ex vivo tissue and biofluid samples, quantification of individual metabolites is often not feasible. Therefore, automated analyses that do not require the assignment of spectral peaks to particular compounds are used [73]. Although they are of high diagnostic value, these methods make it harder to link the acquired data to the underlying metabolic pathways [74].

Conclusion

Glaucoma remains a poorly understood disease, with a small range of therapeutic options. Metabolomics has the potential to provide biomarkers that can be used as an add-on to the currently available diagnostic, classification, and progression detection tools. Furthermore, this technology can provide further knowledge regarding the pathophysiology behind this disease, which could lead to new drug development research lines. The future of medicine is moving towards a personalized approach, and metabolomics will be an important tool in patient profiling and precision medicine.

Disclosure Statement

The authors declare no conflict of interests.

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