EDITORIAL

The Metabolic Shift: Unraveling the Potential of the Ketogenic Diet in Glaucoma Management

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In recent years, the ketogenic diet (KD) has gained significant attention for its potential health benefits beyond weight management, especially in the field of neurodegenerative disorders. Among its various applications, emerging research suggests that the KD may hold promise in the realm of neuroprotection and glaucoma management. While traditional and scientifically proven approaches to glaucoma treatment primarily focus on intraocular pressure reduction, recent studies have explored the influence of dietary factors on disease progression. There has been a keen interest in the neuroprotective effects of the KD in glaucoma following clinical trials demonstrating its positive impact on quality of life in patients with neurodegenerative disorders, including epilepsy, multiple sclerosis, Parkinsonism, and Alzheimer's disease.[1–7] While the empirical evidence is encouraging, there are several myths, misconceptions, and controversies around its use in glaucoma. This editorial delves into the scientific evidence surrounding the KD's potential effects on glaucoma and its implications for patient care and future research directions.

Why is a Ketogenic Diet Neuroprotective?

The KD is a high-fat, modest protein, and low carbohydrate dietary regimen that relies on the substitution of ketone bodies for glucose as the major source of energy for the neural tissues. The use of ketone bodies produces more adenosine triphosphate per unit of oxygen consumed, as compared to glucose. This is postulated to result in improved mitochondrial functioning, reduction of free radicals, decreased apoptosis, and consequent retardation of neuronal degeneration.[1] Moreover, ketone bodies like β-hydroxybutyrate (BHB), acetoacetate (ACA), and acetone are potentially neuroprotective and may impact specific inflammatory proteins, transcription factors, and reactive oxygen species. They are also presumed to protect mitochondria and influence both epigenetic modifications and the intestinal microbiota. Restriction of carbohydrates is thus gaining considerable interest as a potential therapeutic approach for neurodegenerative diseases of the eye.[8,9]

The other mechanisms[2,10,11] of action include decreased inflammation and reactive oxygen species, increased dopamine production, glutamine conversion into γ-aminobutyric acid, as well as decreased glucose and insulin concentrations, and improved neuronal metabolism. Increased mitochondrial biogenesis, remyelination, decreased amyloid plaques, and microglia activation are also important associations of the KD. Induction of autophagy, decreased microglia activation, and modulation of the gut microbiome also modify the inflammatory response.

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Is There Evidence for Neuroprotection in Glaucoma?

There is empirical evidence that restricted carbohydrate consumption can enhance mitochondrial function in neurodegenerative diseases.[12] Harun-Or-Rashid et al. reported that the axonal metabolic decline in murine glaucoma could be reversed by the upregulation of monocarboxylate transporters and mitochondrial biogenesis using a KD.[13] In a similar rat model, Thaler et al. reported that ACA and BHB demonstrated a significant dose-dependent neuroprotective effect on retinal ganglion cells (RGCs).[14] However, the dietary protocols in these studies were extremely strict, with 0.1% carbohydrate and 90% fat, which is not a realistic protocol for a long-term human diet.[12,15,16] This is because KD results in appetite suppression and has an adverse organoleptic profile with several side effects on the gastrointestinal system.

In a large population-based, real-world observational study, Hanyuda et al.[1] followed up with 185,638 participants biennially (from 1976–2016, 1986–2016, and 1991–2017) to evaluate the potential long-term impact of low-carbohydrate dietary patterns and primary open-angle glaucoma. They reported that there was no association between low-carbohydrate diets and the risk of POAG. They postulated that the overall null association could be because of the potentially detrimental effects of higher fats and proteins from animal sources.

However, the authors also found that a stronger adherence to a low-carbohydrate diet, along with high consumption of fat and protein derived from vegetable sources, demonstrated a moderate reduction in the risk of primary open-angle glaucoma accompanied by early paracentral visual field (VF) loss. They found that the substitution of carbohydrates for fat and protein from vegetable sources was associated with a 20% lower risk of initial paracentral VF loss. The latter arises from a loss of retinal ganglion cells in the

maculopapillary bundle. These RGCs are vulnerable to both vascular dysregulation and vascular dysfunction, and presumably, the KD helps protect these cells.[17–20] No similar correlation was found between this dietary pattern and POAG, which is characterized solely by peripheral VF loss.

This ambiguity in response could possibly be because the low-carbohydrate diet, although a practical alternative to a KD in the long term, may not demonstrate all the benefits of the latter.

What are the Implications for Glaucoma Patients?

The KD holds promise as a nonpharmacological approach for neuroprotection in various neurologic conditions, including glaucoma and optic nerve disorders. Emerging evidence suggests its potential in preserving retinal ganglion cells and improving functional outcomes. Despite the neuroprotective effects of the KD, there are challenges and controversies that warrant consideration.[12,15,16] Rational diet composition, long-term safety, and individual variability in response need further exploration to optimize the therapeutic potential of the ketogenic, or indeed the low carbohydrate, diet.

Therefore, further real-world evidence is needed to elucidate the underlying mechanisms, optimize diet composition, and establish long-term safety and efficacy profiles before it can be advocated as part of glaucoma therapy. That said, the beneficial effects of a plant-based, low-carbohydrate diet may help in better euglycemic control, with an indirect effect on glaucoma incidence and progression. Continued scientific inquiry and clinical investigations will provide valuable insights into the utility of the KD as a therapeutic strategy for neuroprotection in glaucoma.

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