Physical exercise and glaucoma: a review on the roles of physical exercise on intraocular pressure control, ocular blood flow regulation, neuroprotection and glaucoma-related mental health

Ming Ming Zhu,1 Jimmy Shiu Ming Lai,1 Bonnie Nga Kwan Choy,1 Jennifer Wei Huen Shum,1 Amy Cheuk Yin Lo,1 Alex Lap Ki Ng,1 Jonathan Cheuk Hung Chan1 and Kwok Fai So1,2,3,4

1Department of Ophthalmology, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China
2School of Biomedical Sciences, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China
3State Key Laboratory of Brain and Cognitive Sciences, The University of Hong Kong, Hong Kong SAR, China
4GHM Institute of CNS Regeneration, Ministry of Education CNS Regeneration Collaborative Joint Laboratory, Jinan University, Guangzhou, China

ABSTRACT.
The benefits of physical exercise on health and well-being have been studied in a wide range of systemic and ocular diseases, including glaucoma, a progressive optic neuropathy characterized by accelerated apoptosis of retinal ganglion cells (RGCs). Elevated intraocular pressure (IOP) and insufficient ocular perfusion have been postulated to be the two main theories in glaucoma development and progression. The effects of exercise in these two aspects have been demonstrated by numerous researches. A review in 2009 focusing on these two theories concluded that exercise results in transient IOP reduction but an inconsistent elevation in ocular perfusion. However, the majority of the studies had been conducted in healthy subjects. Over the past decade, technological advancement has brought forth new and more detailed evidence regarding the effects of exercise. Moreover, the neuroprotective effect of exercise by upregulation of neurotrophin and enhancement of mitochondrial function has been a focus of interest. Apart from visual impairment, the mental health issues in patients with glaucoma, which include anxiety and depression, should also be addressed. In this review, we mainly focus on publications from the recent years, so as to provide a comprehensive review on the impact of physical exercise on IOP, ocular perfusion, neuroprotection and mental health in patients with glaucoma.

Key words: glaucoma – intraocular pressure – mental health – neuroprotection – ocular perfusion – physical exercise

Introduction
Glaucoma is a common vision-threatening condition characterized by accelerated apoptosis of RGCs (Nickells 1996), leading to progressive visual field constriction and eventually loss of vision. It has been the leading cause of irreversible blindness in the world, accounting for 12.3% of total blindness (World Health Organization: Prevention of Blindness and Visual Impairment). Currently, there are 61 million people suffering from glaucoma globally, and the number is estimated to go up to 80 million by 2020 [World Health Organization (WHO): Consultation on Public Health Management of Chronic Eye Diseases: Report of a WHO consultation, 2011].

Elevation of IOP is a well-known modifiable risk factor for glaucoma development and progression. Intraocular pressure elevation leads not only to mechanical compression of the optic nerve fibre bundles, resulting in discontinuity of axonal transport (Yamamoto & Kitazawa 1998), but also to restriction of the blood supply to the optic nerve when the IOP is greater than the...
exercise benefits glaucoma control, will also be discussed.

Methods of Literature Search
The literature was searched through PubMed and Google with the following keywords: ‘exercise’ and ‘intraocular pressure’; ‘exercise’ and ‘ocular perfusion’; ‘exercise’ and ‘neuroprotection’; ‘exercise’ and ‘BDNF’; ‘exercise’ and ‘mitochondria’; ‘glaucoma’ or ‘exercise’ and ‘psychology’; ‘scuba diving’ and ‘IOP’ or ‘glaucoma’ or ‘ocular complication’; and ‘Bungee Jumping’ and ‘IOP’ or ‘glaucoma’ or ‘ocular complication’.

All articles published between 1970 and 2016 and their references were retrieved. To avoid duplication with the text in the review published in 2009 (Risner et al. 2009), in the sections of effect of exercise on IOP and OPP, we mainly focused on the articles that were not included the published review (Risner et al. 2009). Only the relevant papers with abstracts and reference lists in English were included.

Physical Exercise and IOP Control
Physical exercise can be classified as dynamic and isometric, depending on whether or not noticeable changes in the muscle length are present during muscle contraction. Dynamic exercise involves a change in muscle length, for example jogging and cycling, while isometric exercise is performed in static positions, such as weightlifting and handgripping. Risner et al. (2009) reviewed the published literature regarding the effect of exercise on IOP and demonstrated that IOP decreased after dynamic exercise, while the effect of isometric exercise on IOP was more controversial. This was the first review in the literature to assess the effects of exercise on IOP. In 2016, a review by McMonnies evaluated the influences of exercise on IOP, which focused on the possibility of exercise-induced IOP elevation, aiming to provide evidence to patients who are at risk of developing glaucoma on how to avoid damage from inappropriate exercise (McMonnies 2016). In our review, we will summarize the recent evidence regarding the impact of exercise on IOP, focusing on both the beneficial and the possible adverse effects.
decrease in blood pH might contribute to the IOP reduction effect (Marcus et al. 1970; Kielar et al. 1975; Smith et al. 1989). The effect seemed to wear off shortly with time, and the IOP-lowering effect was only modest in most of the reports, ranging from 0.56 mmHg to 5.6 mmHg.

**Sedentary versus active subjects.** There is evidence that dynamic exercise has a more significant IOP reduction effect in sedentary than in active populations. A meta-analysis in 2014 demonstrated a twofold IOP reduction in sedentary populations compared to their active counterparts (Roddy et al. 2014). Ozmerdivenli et al. (2006) found that running on a treadmill for 30 min induced a significant IOP reduction of 4.64 mmHg in sedentary people, and a smaller reduction of 2.92 mmHg in sportsmen, within 3 min after exercise. In Dane et al. (2006a) study, the immediate IOP reduction was only found in the sedentary group but not in athletes, after 5 min on a treadmill, at a 70% maximum rate of oxygen consumption (VO₂max). However, subsequent research by the same group revealed that the IOP decreased as well in athletes, 30 min after a 5-min dynamic exercise with the same intensity, and the effect lasted for 2 hr (Dane et al. 2006b).

**Glaucoma subjects.** There is limited evidence regarding the IOP reduction induced by dynamic exercise in patients with glaucoma. In 1995, Qureshi reported that the magnitude and duration of exercise-induced IOP reduction could be more prominent in patients with glaucoma not receiving treatment, compared to normal subjects. In Natsis et al. (2009) study, 10 min of moderate-intensity cycling on a bicycle ergometer induced an additional IOP reduction (2–3 mmHg) in patients with glaucoma on antiglaucoma agents including β-blockers, α2-agonists and prostaglandin analogues (PGA). An additional and significant IOP reduction of 2.78 mmHg after 10 min of exercise on a cycle ergometer at an intensity of 20% maximum watt (Wmax), and 4.90 mmHg after 5 min of exercise at 60% Wmax, was also observed in patients with glaucoma on topical PGA instillation alone (Yang et al. 2014). Therefore, dynamic exercise induced an IOP reduction in patients with glaucoma, which was independent of the use of antiglaucoma agents. Yokota et al. (2016) reported that the average IOP in patients with primary open-angle glaucoma (POAG) who exercised for more than 30 min per week (type and intensity of exercise not specified) was 1.5 mmHg lower than that in patients who did not exercise regularly; they also showed that habitual exercise halted the progression of visual field defects.

However, dynamic exercise is not always effective in lowering IOP. Exercise may cause remarkable IOP elevation in pigment dispersion glaucoma (PDG). The underlying mechanism is supposed to be exercise-induced iris concavity (Jensen et al. 1995; Haargaard et al. 2001), which enhances mechanical rubbing of the iris against the zonular bundles, resulting in iris pigment release (Ritch 1996). Schenker reported a 32-year-old man with pigment dispersion syndrome (PDS) who suffered from IOP elevation to 25 mmHg in his right eye and 39 mmHg in the left in the left after playing basketball (Schenker et al. 1980). Haynes et al. (1995) also reported a patient with PDS who suffered from a sudden rise in IOP after playing basketball. Mastropasqua et al. (1995) reported an average IOP increase of 30 mmHg in three PDS subjects after 30 min of jogging on a treadmill. Gallenga et al. (1997) reported that 30 min of jogging on a treadmill increased IOP in patients with PDS by an average of 11 mmHg, and the IOP did not decrease 1 month afterwards. Smith et al. (1989) evaluated IOP variation in 10 patients with pigmentary glaucoma after exercise, in which the IOP increased by 6–7 mmHg 15 min after exercise, but returned to baseline by 30 min. Haynes and colleagues showed that 45 min of jogging was likely to induce pigment dispersion in patients with PDG and PDS. However, the increase in pigment did not increase IOP in most PDG or PDS subjects (Haynes et al. 1992). The exercise-induced IOP increase could be prevented by pilocarpine drops before exercise (Schenker et al. 1980; Haynes et al. 1990, 1992, 1995), while the effect of alpha-adrenergic blocking agents was controversial (Haynes et al. 1995; Mastropasqua et al. 1995).

**Myopic subjects.** Myopia, especially high myopia, is a known risk factor for POAG (Mitchell et al. 1999; Perdicchi et al. 2007; Xu et al. 2007; Lee et al. 2008). Exercise-induced IOP reduction was found to be markedly greater in POAG patients with high myopia (≥ –6D) compared with the nonhighly myopic and emmetropic groups (Yang et al. 2014). The potential mechanism remains unclear. Yang et al. (2014) hypothesized that the structural and functional changes in eyeballs with longer axial lengths, for example the insufficient perfusion to the choroid and the retina, might result in a defective autoregulatory response and a more significant fluctuation in IOP after exercise.

**Effect of exercise intensity and duration on dynamic exercise-induced IOP reduction**

Whether exercise intensity or duration is more crucial in determining the amount of exercise-induced IOP reduction remains controversial. As early as 1995, Qureshi conducted a study on the effects of mild (walking), moderate (jogging) and intense exercise (running) on IOP and found that IOP reduction in the three types of exercises was 2.43 mmHg, 3.85 mmHg and 4.0 mmHg, respectively, indicating that increasing exercise intensity is associated with more significant IOP reduction (Qureshi 1995). Recently, Rufer et al. (2014) reported that 10 min of cycling on a cycle ergometer significantly decreased IOP by 2.3 mmHg, but the effect was not enhanced by prolonging the exercise period to 20 and 30 min, indicating that prolonging the duration did not intensify the amount of IOP reduction. Yang et al. (2014) also suggested a more significant IOP reduction effect with more intensive exercise. Conte’s group found that both high-intensity-interval training (HIT) and continuous moderate exercise (CME) were effective in IOP reduction in young healthy subjects. However, the effect of HIT could last for 10 min, while that of CME could only last for 5 min, indicating that HIT produced a more sustained effect on IOP reduction (Conte et al. 2014). On the contrary, comparing 30 min of running and 30 seconds of Wingate test, an anaerobic dynamic exercise by riding on cycle ergometer as fast as possible, suggested that running, a type of CME, had a more robust effect on IOP reduction than Wingate, a short burst of intensive exercise (Ozmerdivenli et al. 2006). The above evidence
suggests that the more intensive the exercise, the more significant the IOP reduction, and that the duration of exercise seems to be a less important factor.

**Exercise conditioning and IOP**

In 1987, Passo et al. reported that four months of exercise conditioning (maximal aerobic exertion) reduced baseline IOP from 14.3 mmHg to 13 mmHg. They also reported that 3 months of aerobic exercise training on bicycle ergometer at an intensity of 70–85% heart rate lowered IOP from 23.8 mmHg to 19.2 mmHg in 13 glaucoma-suspect patients, and the IOP reduction effect wore off after cessation of training for 3 weeks (Passo et al. 1991). The long-term effect of exercise conditioning on IOP in these subjects was continuously monitored for 3 years, and the results showed that the IOP-lowering effect could be maintained at 16 mmHg at the end of 3-year follow-up (Passo et al. 1992). However, there is insufficient evidence on the effect of chronic exercise on IOP to support the conclusion that exercise can achieve sustained IOP-lowering effect to be considered an alternative treatment for glaucoma, but the possible benefits of regular exercise should be evaluated by further studies.

**Types of dynamic exercises with potential adverse effects on IOP**

**Swimming.** Swimming is one of the most popular dynamic exercises. However, the use of swimming goggles might potentially increase IOP. A small but significant IOP elevation of 2.3 mmHg was observed immediately after swimming goggles were put on, and remained elevated until they were taken off (Ma et al. 2007). Morgan et al. (2008) reported a higher IOP rise of 4.5 mmHg during goggles wear, which was associated with a smaller goggles/face area. The transient IOP elevation did not induce any loss in the retinal nerve fibre layer in normal subjects (Ma et al. 2007), but it could further induce RGC loss in an already compromised optic nerve as in glaucoma. In 2010, Kang et al. reported a case of NTG progression, possibly as a result of wearing swimming goggles four times per week, each session lasting for 60 min, over a 15-year period. In this patient, the IOP rose by around 20 mmHg above baseline, 3 min after the goggles were applied, and 20 min later, the pressure increase was even higher than 30 mmHg in either eye (Kang et al. 2010). Given the above evidence, it seems that wearing swimming goggles increases IOP slightly and transiently in normal subjects, but remarkably in patients with glaucoma, and causes permanent damage. Patients with glaucoma should thus be warned against the indiscriminate use of swimming goggles.

**Scuba diving.** Scuba diving is a kind of underwater diving where the divers breathe underwater with the help of self-contained breathing equipment. Contrary to swimming goggles, the diving mask has not been found to induce any increase in IOP (Goenadi et al. 2016). As early as the 1970s, Kalthoff et al. (1975) reported that under excessive pressures of 2 and 4 atm, the IOP decreased by 2–3 mmHg. Their group also pointed out that glaucoma patients with shallow chambers stood the high risk of acute IOP rise during ascent (Kalthoff & John 1976). Besides IOP variation, Macarez et al. (2005) found that people with iterative diving had more visual field defects. If pressure within the scuba mask is not equalized with the external pressure, the pressure changes during descent and ascent may cause ocular barotrauma, which could induce visual impairment and visual field loss. Rudge (1994) reported ocular barotrauma that was attributed to increased pressure within the mask during ascent. Yeoh et al. (2008) reported that sinus barotrauma caused by pressure changes during diving also induced visual impairment. Gunn & O’Hagan (2013) reported a healthy woman who suffered from reversible and transient visual impairment and visual field changes caused by sphenoid sinus barotrauma after scuba diving. Mowatt & Foster (2013) reported a similar but more serious case of a sphenoidal mucocelle that expanded during scuba diving, which resulted in visual impairment. Therefore, scuba diving does not seem to be a suitable type of sport for patients with glaucoma, but the diving mask may be a safer alternative than the regular swimming goggles for such patients, because it does not cause IOP increase.

**Bungee jumping.** Bungee jumping involves jumping and diving in a head-down position from height, with a long elastic cord tied around the body to keep it from hitting the ground. During the free fall, the body would be suddenly decelerated when the cord reaches its maximum stretch, but inertia causes the blood within the vessels to keep rushing forward to the top of the head, resulting in an increase in hydrostatic pressure in the blood vessels of the eye (Simons & Krol 1994). Both the head-down position and force of the impact will theoretically increase IOP, especially in patients with shallow anterior chambers, although IOP spikes during bungee jumping have not been reported. However, it has been widely reported that bungee jumping would induce ocular complications, including subconjunctival haemorrhage (Chan 1994; David et al. 1994), preretinal and retinal haemorrhage (David et al. 1994; Filipe et al. 1994; Jain & Talbot 1994; Curtis & Collin 1999), macular oedema (David et al. 1994; Van Rens 1994) and foveal haemorrhage (Chan 1994; Habib & Malik 1994; Innocenti & Bell 1994; Jain & Gaynon 2007), leading to temporary or permanent visual impairment. Therefore, the potential risks of bungee jumping should be warned to patients with glaucoma.

Base on the case reports, swimming goggles wear, scuba diving and bungee jumping are potentially hazardous to patients with glaucoma. However, more clinical studies are necessary to derive a definitive conclusion to offer evidence-based advice to our patients.

**Isometric exercise and IOP**

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The effect of isometric exercise on IOP is inconsistent from a previous review (Risner et al. 2009). Bakke et al. (2009) first monitored the real-time IOP fluctuation continuously during a 2-min handgripping. The IOP was found to gradually increase in parallel with systemic blood pressure (BP) (Bakke et al. 2009). Castejon et al. (2010) also found that the IOP rose significantly by 31% to 46% during squatting and by 18% to 35% during handgripping. Polska et al. (2007) reported a small but significant IOP increase at the first minute of squatting. Experiments on both humans and animals found that the IOP rise in isometric exercise was parallel with the change in BP and partly influenced by partial pressure of
carbon dioxide (measured by the transcutaneous route) (Castejon et al. 2010).

The IOP elevation induced by isometric exercise was reported to be related to the Valsalva manoeuvre. (Vieira et al. (2006) reported a significant IOP increase during bench pressing, and the increase was as high as 10 mmHg in some participants when they were asked to hold their breath. The IOP elevation could be partly relieved when the Valsalva manoeuvre was discontinued (Vieira et al. 2006). Rufer et al. (2014) found there was no influence of isometric exercise on IOP as long as a Valsalva manoeuvre was avoided. During Valsalva manoeuvre, the central venous pressure is increased followed by obstruction of venous reflux, resulting in elevation of episcleral venous pressure (EVP). Intraocular pressure is calculated as $F/C = EVP$, where $F$ = aqueous fluid formation rate and $C$ = outflow rate. Therefore, the increase in EVP directly induces IOP elevation.

In studies by Lasta et al. (2012), Tittl et al. (2005) and Luksch et al. (2006), the IOP was unchanged or insignificantly increased during and after 6 min of squatting. No change in IOP was detected after 1 min of handgripping, repeated for three times (Zhang et al. 2012). A contradicting result was observed by Rajkumar Banner & Satyavati (2015). They reported an IOP reduction of 1.82 and 3.11 mmHg, respectively, 5 min after handgripping at 20% and 40% of the predetermined maximum voluntary contraction (Rajkumar Banner & Satyavati 2015). Although there is evidence suggesting the association between isometric exercise and IOP elevation, it is difficult to conclude that isometric exercise does actually aggravate glaucoma and accelerate vision loss, because it may also be beneficial in increasing ocular perfusion, and also because the exercise-induced IOP elevation is usually transient, returning to normal only several minutes after exercise (Bakke et al. 2009; Castejon et al. 2010).

Yoga and IOP
Yoga, which is believed by some to be a viable alternative to conventional medical therapy (Nayak & Shankar 2004), is one of the most popular exercises in India and is now sweeping across the world. Some of the Yoga positions can be regarded as isometric exercises and may involve body inversion, which was found to have a severe impact on IOP (Baskaran et al. 2006; Jasien et al. 2015).

Jessica et al. investigated the IOP changes in four common head-down Yoga positions, namely Adho Mukha Svanasana, Uttanasana, Halasana and Viparita Karani (Fig. 1), in patients with POAG and in normal subjects and found that all these postures induced an IOP elevation of 16% to 70% in both patients with POAG and normal subjects, although there was no statistically significant difference in IOP rise in the two groups (Jasien et al. 2015). Baskaran et al. (2006) demonstrated an immediate twofold increase (around 15 mmHg) in IOP during the period of performing Sirsasana (headstand posture) and the IOP return to near baseline level as soon as the sitting posture was resumed. Although the results from this study did not suggest that the increased IOP was associated with a higher prevalence of development of ocular hypertension or glaucoma in normal subjects (Baskaran et al. 2006), there are evidences that the transient IOP elevation in Sirsasana contributes to disease progression in patients with glaucoma. A progressive optic neuropathy and visual field loss were reported in a 46-year-old patient with NTG (Gallardo et al. 2006) and in a 47-year-old woman with history of congenital glaucoma (de Barros et al. 2008), after practising Sirsasana daily for years. As mentioned before, IOP is closely associated with EVP. The elevation of EVP has been confirmed in both animal (Lavery & Kiel 2013; Abe et al. 2015) and human studies (Friberg et al. 1987) during head-down position. In addition to EVP, choroidal thickness might increase in head-down position due to the increase in intracranial cerebrospinal fluid pressure, which indirectly influences the choroid veins that drain into superior ophthalmic vein and finally into intracranial cavernous sinus (Jonas et al. 2014; Jasien et al. 2015). Therefore, these head-down postures might be a risk factor for glaucoma progression and should be avoided in people with or at high risk of glaucoma.

**Physical Exercise and Ocular Perfusion**
Pathological elevation of IOP is well known to be the main risk factor for glaucoma development and progression. However, many patients suffer from glaucoma progression despite a normal IOP. A vascular aetiology has been hypothesized to play a critical role in glaucoma progression (Lee et al. 2017). The Leuven Eye Study conducted by Abegao Pinto et al. (2016) found that patients with glaucoma had lower retrobulbar velocities compared to the normal subjects. Portmann et al. (2011) demonstrated that the choroidal blood flow (ChBF) in POAG and ocular hypertension was lower, compared with that in the control subjects. The Egna-Neumarkt Study identified that low diastolic perfusion pressure was an important risk factor for POAG (Bonomi et al. 2000). Evidence from epidemiological surveys also suggested that subjects with low OPP were more likely to develop glaucoma and suffer from disease progression (Quigley et al. 2001; Leske et al. 2007).

The OPP is the net pressure gradient representing blood flow to the eye, which refers to the relation between systemic BP and IOP. The OPP is calculated as $2/3$ mean arterial pressure (MAP) – IOP, where $MAP = diastolic BP + 1/3$ (systemic BP – diastolic BP) (Riva et al. 1985). The EPIC-Norfolk eye study investigated 5650 participants and demonstrated a lower level of physical activity was associated with a lower OPP (Zhang et al. 2012). Although results from the published research are consistent that physical exercise remarkably induces OPP elevation, the association between OPP and blood flow to the posterior pole of the eye is complex due to the presence of autoregulation. Autoregulation is a mechanism that maintains constant blood flow despite changes in OPP. When the OPP increases, the ocular blood supply has a regulatory mechanism to modulate blood flow to avoid significant rise in ocular perfusion, and vice versa. The review published in 2009 concluded that autoregulation occurs in both dynamic exercise and isometric exercise, resulting in the unparalleled elevation of OBF and OPP (Risner et al. 2009). Most of the results from the past ten years were consistent with this conclusion.
Currently, the studies on this area are merely focusing on the transient impact of acute exercise on OBF. There is a lack of research on whether exercise conditioning has sustained effect on OPP or OBF, which is more meaningful in glaucoma control.

Dynamic exercise and ocular perfusion

The OBF comprises two main systems: the retinal circulation which is characterized by a low blood flow with a high oxygen extraction rate of 38%, and choroidal circulation with high blood flow, supplying 85% of the total OBF, but a relatively low arterio-venous oxygen difference of only about 3% (Delaney & Van De Voorde 2000; Lu & Adamis 2006). Iester et al. (2007) found that there was no change in retinal blood flow (measured by a Heidelberg retina flowmeter) after exercise due to the autoregulation in young healthy subjects. An elevation in OPP and blood flow (measured by colour Doppler imaging) at the ophthalmic artery but not in the central retinal artery or short posterior ciliary arteries was demonstrated after 30 min of exercise on the treadmill by Kozobolis et al., suggesting that autoregulation was involved in both retinal and choroidal circulations (Kozobolis et al. 2008). Okuno’s group found that the retinal OBF [measured by scanning laser Doppler flowmetry (LDF)] increased immediately after 6 min of Master’s double two-step test, but returned to the baseline at 30 min postexercise, while the choroidal–retinal blood flow [measured by laser speckle flowgraphy (LSFG)] continued to increase for 60 min (Okuno et al. 2006). The difference in the response of blood flow indicated a stronger autoregulatory effect in the retina. However, there is evidence disproving the theory of autoregulation in the retinal and choroidal vessels during dynamic exercise (Hayashi et al. 2011). In Hayashi et al. (2011) study, blood flow in the retinal and choroidal vessels (measured by LSFG) increased remarkably with dynamic exercise and the elevation was associated with exercise intensity. However, they did not suggest an effect on the retinal arterioles (Hayashi et al. 2011). Twenty minutes of biking at high intensity (HR = 140 beats/min) increased mean BP by 10%, OPP by 16.2% and the averaged pulsatile OBF (measured by OBF Tonograph system) by 18% (Lovasik & Kergoat 2004). Another study also found that stereometric optic nerve head (ONH) parameters (measured by Heidelberg Retina Tomograph II), such as rim area, cup area, cup/disc area ratio, rim/disc area ratio and rim volume, increased with OPP during cycling at an intensity which raised systolic BP by at least 30 mmHg (Saarelä et al. 2013).

Isometric exercise and ocular perfusion

It has been reported that isometric exercise increases OPP, but also has a vasoconstrictive effect, which causes narrowing of the retinal venous and arterial diameters (measured by Zeiss retinal vessel analyser) (Luksch et al. 2006). However, there has been evidence showing that the choroidal circulation has an autoregulatory response to isometric exercise in the normal population. Ocular perfusion pressure (OPP) increased by 28% and 45% from baseline at 1 and 2 min during squatting, but the ChBF (measured by LDF) did not increase (Khayi et al. 2011). Schmidl et al. demonstrated that the increase in the ChBF (measured by LDF) after 6 min of squatting was 10%, which was less pronounced than the 58% increase in OPP (Schmidl et al. 2012a). Six-minute squatting was also found to increase subfoveal ChBF (measured by LDF) by 10%, whereas the OPP was increased by as high as 85% (Tittl et al. 2005). Metelitsina et al. (2010) reported that 3 min of handgripping increased OPP by 20% but had no effect on choroidal circulation (measured by LDF). Similar results were observed in Polska’s study, which showed a squatting-induced OPP increase of 36%, but only a 9% increase in ChBF (measured by LDF) (Polska et al. 2007). Furthermore, changes in ChBF were found to be more dependent on IOP elevation compared to exercise-induced changes in MAP, indicating that the autoregulatory response of ChBF was more dependent on changes in MAP (Polska et al. 2007). However, it seems that the autoregulation of choroidal circulation in patients with glaucoma is less active. Choroidal blood flow (measured by confocal LDF) response to 90 seconds of isometric exercise with a Martin’s vigorimeter in the POAG group was twofold stronger than that in the normal subjects (Portmann et al. 2011). Also, Ciulla et al. (2017) found a negative relationship between IOP and OBF in hypertensive patients but a weak positive relationship in nonhypertensive patients, indicating the disorder of vascular autoregulation caused by hypertension may contribute to glaucoma pathology. Whether such dysfunction is one of the pathogenic factors in patients with glaucoma requires further evidence.

Autoregulation was also found in the ONH, as evidenced by a 30% increase in OPP, but there was no corresponding increase in ONH blood flow (measured by LDF) after three sessions of 2-min handgripping (Boltz et al. 2013a). Boltz et al. (2013a) demonstrated that 6 min of squatting increased OPP by 84% and the ONH red cell flux (measured by LDF) by 27%. Similar to the results in ChBF from Polska et al. (Polska et al. 2007), ONH blood flow was found to correlate with IOP more than MAP. A correlation between ONH blood flow (measured by LDF) and MAP was found only when the IOP was lower than 25 mmHg (Boltz et al. 2013b). Schmidl et al. (2012a) demonstrated that there was no change in the response to 6-min squatting in choroidal and ONH blood flow (measured by LDF) when the increase in OPP was, respectively, less than 66% and 70% above the baseline. Chiquet et al. reported that 2-min handgripping
induced a 43% increase in OPP and an increase of 19% in blood flux (measured by LDF) in the ONH (Chiquet et al. 2014). Moreover, the effect of autoregulation appears to vary significantly among subjects due to individual variations. In Chiquet et al.’s study, the ONH blood flow was demonstrated to increase in parallel with OPP in only six of 14 subjects, but remained stable in the remaining subjects despite a significant elevation in OPP (Chiquet et al. 2014). However, repeating 1-min handgripping for three times was found to significantly increase both OPP and retina/ChBF (measured by pseudo-continuous arterial spin labelling technique) by 25% in four healthy volunteers (Zhang et al. 2012).

In contrast to the different responses of IOP to dynamic exercise and isotonic exercise, the response of ocular perfusion (although the measurement methods are different) to both types of exercise was similar. The OPP was elevated in both dynamic exercise and isotonic exercise, although the increase was limited due to autoregulatory response.

Mechanism of ocular blood flow alteration with exercise

Regulation of OBF involves the interplay of vasodilators (such as nitric oxide) and vasoconstrictors (endothelin). Nitric oxide (NO) and endothelin-1 (ET-1), but not angiotensin II, were found to be involved in the regulation of exercise-induced OBF, although the exact underlying mechanism remains unknown. The NO metabolites increased after 6 min of Master’s double two-step test, which was paralleled by the rise of retinal blood flow (Okuno et al. 2006). Nitric oxide was potentially involved in retinal autoregulation during isotonic exercise as the response of the retinal venous diameter to 6-min handgripping was less pronounced after the administration of NO inhibitor (Lasta et al. 2012). The increase in ONH red cell flux during squatting was more significant when ET-1 type A (ETa) receptors were inhibited by BQ123, the ETA receptor antagonist (Bolzt et al. 2013a). ET-1 was also found to be involved in the retinal and ChBF regulation during isotonic exercise, while angiotensin II had no effect (Fuchs-Nagler-Mayr et al.

03; Luksch et al. 2006). In addition, exercise is known for its antioxidating ability (Thirupathi & de Souza 2017), while antioxidants were found to be associated with increase in OBF (Harris et al. 2017).

The summary of the effect of different types of exercise on IOP and OBF is shown in Tables 1 and 2.

Neuroprotection of Physical Exercise in Glaucoma

The ongoing neurodegeneration of RGCs, resulting from pathological elevation of IOP, insufficient ocular perfusion or possibly other pathogenic factors, leads to visual field damage in patients with glaucoma. Recently, an increasing number of neuroprotective agents are being investigated, although none of these neuroprotectants seem to achieve a definitive clinical effect.

Physical exercise has been investigated to promote neuronal plasticity and enhance resistance to neurodegeneration in the brain, spinal cord and cardiovascular system in both humans and experimental animals (Michelini & Stern 2009; Alvarez-Mejia et al. 2015; Sandrow-Feinberg & Houle 2015; Chali et al. 2016; Hutterrauch et al. 2016; Li et al. 2016; Otsuka et al. 2016). Limited but consistent evidence of neuroprotection from exercise in animal models has been found in various retinal degenerative diseases, although the type and protocol of exercise were inconsistent and not comparable in these studies. In diabetic retinopathy, exercise on the treadmill for 30 min/day, 5 days/week for 6 weeks was found to ameliorate diabetes-induced apoptosis in retinal cells (human or animal model) (Kim et al. 2013). After 4 weeks of exercise (pre-conditioning of exercise for 2 weeks and additional 2 weeks of exercise after light exposure) at intensity of 10 metres/min, at a frequency of 5 days/week, 60 min/day, was found to be effective in preserving function and count of photoreceptors in light-induced retinal degenerative models in mice (Lawson et al. 2014; Chrenek et al. 2016). Voluntary exercise using running wheel for 6 weeks was also suggested to protect photoreceptor in the retinitis pigmentosa model in mice (Hanif et al. 2015). The underlying mechanisms of how exercise induces neuroprotection include upregulating neurotrophin expression, such as brain-derived neurotrophic factor (BDNF), enhancing mitochondrial function and reducing inflammation. In this review, we mainly focus on its effect in BDNF expression and mitochondrial function.

Exercise and BDNF expression

The first research on exercise-induced neuroprotection in RGCs was conducted on acute IOP elevation model in mice in 2014 by Chrysostomou et al. (2014). The vulnerability of aged RGCs facing IOP elevation to 50 mmHg for 30 min was evaluated by electroretinogram and was shown to be reversed by 60-min daily swimming for 5 weeks before and 1 week after IOP elevation (Chrysostomou et al. 2014). Recently, the original research team of the above study further proved that this protective role was mediated by increasing BDNF expression in the retina (Chrysostomou et al. 2016).

Although there are no additional published literatures directly focusing on the role of exercise in neuroprotection of RGCs, plenty of studies have indicated that BDNF, which could be upregulated in the visual system by exercise (Cancedda et al. 2004; Franklin et al. 2006), is essential in halting RGC degeneration. Brain-derived neurotrophic factor (BDNF) was found to promote RGC survival from axotomized RGC degeneration after optic nerve transection via activation of both MAPK and Akt pathways (Nakazawa et al. 2002). Overexpression of BDNF delayed progressive RGC and axonal loss in ocular hypertensive eyes in chronic glaucoma models (Harper et al. 2011; Domenici et al. 2014; Valiente-Soriano et al. 2015; Feng et al. 2016). Upregulation of BDNF expression preserved RGC loss and retina function from ischemia/reperfusion injury caused by acute IOP elevation model (Igarashi et al. 2016), and the effect could be sustained for up to 70 weeks (Ren et al. 2012). Brain-derived neurotrophic factor (BDNF) was also effective in transiently slowing down axotomy-induced RGC loss (Zhang et al. 2005; Zhi et al. 2005; Parrilla-Reverter et al. 2009; Nakatani et al. 2011; Galindo-Romero et al. 2013; Dekeyster et al. 2015; Junyi et al.
Table 1. Summary on the effect of different type and intensities of dynamic exercise in IOP management and ocular blood flow regulation.

<table>
<thead>
<tr>
<th>Exercise type</th>
<th>Exercise protocol</th>
<th>Subjects</th>
<th>IOP reduction</th>
<th>OPP and OBF effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walk</td>
<td>Brisk walk for 1024 m (Hamilton-Maxwell &amp; Feeney 2012)</td>
<td>25 young healthy</td>
<td>−1.4 mmHg</td>
<td></td>
</tr>
<tr>
<td>Treadmill</td>
<td>Running on treadmill for 15 mins (Hong et al. 2014)</td>
<td>25 young healthy</td>
<td>−3.82 mmHg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>At 70% VO_{2max} for 5 mins (Dane et al. 2006a, 2006b)</td>
<td>25 sedentary subjects</td>
<td>−1.72 mmHg (OS)−1.92 mmHg (OD) in sedentary</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24 athletes</td>
<td></td>
<td>no change in athletes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>At 70% VO_{2max} for 30 mins (Ozmerdivenli et al. 2006)</td>
<td>20 sportsmen</td>
<td>−2.92 mmHg in sportsmen</td>
<td></td>
</tr>
<tr>
<td>Exercise on treadmill according to Bruce protocol (Kozobolis et al. 2008)</td>
<td>30 young male healthy subjects</td>
<td></td>
<td>−5.6 mmHg</td>
<td></td>
</tr>
<tr>
<td>Bicycle ergometer</td>
<td>At an intensity of maintaining HR in a range of 50%–70% of HR reserve for 10 mins (Read &amp; Collins 2011)</td>
<td>10 myopes; 10 emmetropes</td>
<td>−1.71 mmHg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. Bicycle ergometer at 20% maximum Watt (Wmax) for 10 mins</td>
<td>POAG subjects:</td>
<td>1. −3.5 mmHg in POAG with HM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 with HM</td>
<td></td>
<td>−1.52 mmHg in POAG with NHM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>29 with NHM</td>
<td></td>
<td>−2.78 mmHg in POAG with NM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>21 with NM</td>
<td></td>
<td>−7.57 mmHg in POAG with HM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Bicycle ergometer at 60% maximum Watt (Wmax) for 10 mins (Yang et al. 2014)</td>
<td>POAG subjects:</td>
<td>2. −4.66 mmHg in POAG with NHM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100 healthy subjects</td>
<td></td>
<td>−4.90 mmHg in POAG with NM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>45 POAG subjects</td>
<td></td>
<td>2 to 3 mmHg after exercise in both healthy without antiglaucoma agents and healthy and POAG subjects with antiglaucoma agents</td>
<td></td>
</tr>
<tr>
<td></td>
<td>At 60–80 W for 10 mins (Natsis et al. 2009)</td>
<td>10 young healthy subjects</td>
<td>−2.7 mmHg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>From 0 to 147 W</td>
<td>8 healthy subjects</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Characterized by (1) HR: &lt;100, (2) 100–120, (3) &gt;120 bpm (Hayashi et al. 2011)</td>
<td></td>
<td>−</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR 140 bpm, for 20 mins (Lovasik &amp; Kergoat 2004)</td>
<td>18 healthy subjects</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR 170 bpm, for 30 mins (Rufer et al. 2014)</td>
<td>21 young healthy subjects</td>
<td>−2.1 mmHg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+Systolic blood pressure more than 30 mmHg, for 24 mins (Saarela et al. 2013)</td>
<td>35 healthy subjects</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stair climbing</td>
<td>20 healthy subjects</td>
<td>−</td>
<td>NO significant change in retinal blood flow</td>
</tr>
<tr>
<td></td>
<td>+BP more than 20% from the baseline, for 3 mins (Iester et al. 2007)</td>
<td></td>
<td>−</td>
<td></td>
</tr>
<tr>
<td>HIT/CME</td>
<td>HIT: walking at 50% HR for 2 mins and running at 80% HR for 1 min</td>
<td>15 young healthy subjects</td>
<td>+OPP by 16.2%; +pulsatile OBF by 18%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CME: 30 min of jogging/running at 60% of HR (Conte et al. 2014)</td>
<td></td>
<td>−</td>
<td></td>
</tr>
<tr>
<td>Master's double two-step test</td>
<td>Master's double two-step test (Okuno et al. 2006)</td>
<td>10 healthy subjects</td>
<td>−</td>
<td>+ OPP; Retinal BF for 15 min; ChBF for 60 min</td>
</tr>
<tr>
<td></td>
<td>For 60 mins (Ma et al. 2007)</td>
<td>30 healthy subjects</td>
<td>+2.63 mmHg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>For 3 mins (Schaub et al. 2006)</td>
<td></td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>


Exercise and mitochondrial function

Mitochondria are organelles located in the cytoplasm that can be considered as energy factory of the cells. Mitochondrial dysfunction is associated with a number of neurodegenerative diseases, such as Alzheimer’s (Cadonic et al. 2016; Cai & Tammineni 2017), Parkinson’s disease (Bueler 2009; Bose & Beal 2016) and glaucoma (Sas et al. 2007; Knott et al. 2008; Kim et al. 2015; Manocha 2016; Shim et al. 2016). A recent epidemiological study on 3430 patients with POAG and 3108 normal subjects suggested that variations in genes coding mitochondrial proteins that commonly existed in patients with POAG (in both subtypes of NTG and hypertensive glaucoma) were not found in normal subjects, suggesting that mitochondria may be involved in the pathogenesis of POAG (Khawaja et al. 2016). The mitochondrial electron transport chain is the main source of intracellular reactive oxygen species (ROS) generation (Lenaz 2001), which activates RGC death (Chrysostomou et al. 2013; Wang et al. 2014). Reactive oxygen species (ROS), in turn, damages mitochondria, resulting in cell death by initiating the opening of membrane permeability transition pore (MPTP) (Kowaltowski et al. 1996), inducing damage to the mitochondrial respiratory chain and mitochondrial DNA mutation (Holllensworth et al. 2000; Lin & Kuang 2014).

Exercise has been shown to be effective in reversing mitochondrial dysfunction and inducing mitochondrial biogenesis. In humans, both HIT and moderate-intensity continuous training were found to relieve lymphocyte mitochondrial dysfunction via increasing membrane potential and enhancing matrix oxidant burden under hypoxic conditions (Tsai et al. 2016). Four-week exercise preconditioning on the free-running wheel was found to prevent hyperglycaemia by enhancing mitochondrial function in skeletal muscles, in a mouse model of type 1 diabetes mellitus (de Carvalho et al. 2016). In the brain, exercise was found to increase resistance to MPTP, improve mitochondrial physiology, reduce ROS production and induce mitochondrial biogenesis (Marques-Aleixo et al. 2015; Taghizadeh et al. 2016). The beneficial effect of exercise on mitochondria potentially acts as a therapy for Alzheimer’s disease, which is a neurodegenerative disease in the brain (Bernardo et al. 2016). Retinal ganglion cells (RGCs) are more sensitive to mitochondrial dysfunction because they have long axons, with a relatively high density of mitochondria, which provides energy to transport proteins to distal axons (Barron et al. 2004). Therefore, exercise-induced mitochondrial enhancement is potentially helpful in halting RGC loss from glaucomatous damage.

Exercise and the Psychology of Patients With Glaucoma

Like patients with many other chronic diseases, patients with glaucoma are susceptible to anxiety and depression. The reported prevalence of anxiety and depression among patients with glaucoma is 13% to 22.9% and 10% to 16.4%, respectively (Mabuchi et al. 2008; Wang et al. 2012; Yochim et al. 2016; Zhou et al. 2013). In a recent study from Singapore, the reported incidence of anxiety and depression in patients with glaucoma can be as high as 64% and 30% (Lim et al. 2016). The mental disorders not only have a negative impact on the quality of life of patients, but also promote disease progression, because mental stress was found to increase IOP and induce insomnia (Marc & Stan 2013), and the use of zolpidem, a drug to treat insomnia, was found to increase the risk of glaucoma development (Ho et al. 2015).

The relationship between exercise and mental health has been widely studied, and an increase in physical activity is correlated with less anxiety and depression (De Moor et al. 2006, 2008). Two recent population-based studies involving 204186 and 178867 people, respectively, across more than 30 low- and middle-income countries, and published in 2016 and 2017, demonstrated that depression was associated with low physical activity (Stubbs et al. 2016, 2017). Although there are some opposing views regarding the effects of exercise on anxiety
<table>
<thead>
<tr>
<th>Exercise type</th>
<th>Exercise protocol</th>
<th>Subjects</th>
<th>IOP reduction</th>
<th>OPP and OBF effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Handgripping</strong></td>
<td>For 2 mins (Bakke et al. 2009)</td>
<td>9 healthy volunteers</td>
<td>+4 mmHg</td>
<td>OPP+ 43%; ONHBF: 19%</td>
</tr>
<tr>
<td></td>
<td>For 2 mins (Chiquet et al. 2014)</td>
<td>14 healthy subjects</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td></td>
<td>For 2 mins (Castejon et al. 2010)</td>
<td>17 healthy subjects</td>
<td>+35% IOP from the baseline</td>
<td></td>
</tr>
<tr>
<td></td>
<td>For 3 mins (Metelitsina et al. 2010)</td>
<td>17 dry AMD subjects</td>
<td>−</td>
<td>+OPP by 20%, no increase in ChBF</td>
</tr>
<tr>
<td></td>
<td>1 min of handgripping, repeated for 3 sessions (Zhang et al. 2012)</td>
<td>19 healthy controls</td>
<td>IOP unchanged</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 mins of handgripping at 75% MVC, repeated for 3 sessions (Boltz et al. 2013c)</td>
<td>4 healthy volunteers</td>
<td>−</td>
<td>OPP: +13 mmHg. No change in optic nerve head blood flow</td>
</tr>
<tr>
<td></td>
<td>5 mins of handgripping at (Rajkumar Banner &amp; Satyavati, 2015)</td>
<td>30 healthy male subjects</td>
<td>1. −1.89 mmHg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. −2.42 mmHg</td>
<td></td>
</tr>
<tr>
<td><strong>Squatting</strong></td>
<td>For 2 mins (Castejon et al. 2010)</td>
<td>17 healthy subjects</td>
<td>+46% IOP from the baseline</td>
<td></td>
</tr>
<tr>
<td></td>
<td>For 6 mins (Tittl et al. 2005)</td>
<td>14 nonsmoking subjects with CSC</td>
<td>No significant increase in IOP</td>
<td>+OPP by 85%; +Subfoveal ChBF by 10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14 healthy nonsmoking subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>For 6 mins (Luksch et al. 2006)</td>
<td>12 healthy subjects</td>
<td>No significant increase in IOP</td>
<td>+OPP; −retinal venous and arterial diameter</td>
</tr>
<tr>
<td></td>
<td>For 3 mins (Khayi et al. 2011)</td>
<td>21 OSA patients</td>
<td>−</td>
<td>+OPP by 28% and 45% No increase in ChBF</td>
</tr>
<tr>
<td></td>
<td>For 6 mins (Polska et al. 2007)</td>
<td>28 healthy subjects</td>
<td>−</td>
<td>+OPP by 36%; +ChBF by 9% +OPP by 58%</td>
</tr>
<tr>
<td></td>
<td>For 6 mins (Schmidl et al. 2012b)</td>
<td>15 healthy male subjects</td>
<td>−</td>
<td>+ChBF by 10% +OPP by 84% +ONH red cell flux by 27% Only when IOPs ≤25 mmHg. ONHBF was correlated with MAP</td>
</tr>
<tr>
<td></td>
<td>For 6 mins (Boltz et al. 2013a)</td>
<td>15 healthy subjects</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td></td>
<td>For 6 mins (Boltz et al. 2013b)</td>
<td>40 healthy subjects</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td></td>
<td>For 6 mins (Schmidl et al. 2012a)</td>
<td>96 healthy subjects</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td><strong>Yoga (head-down position)</strong></td>
<td>For 6–7 mins (Lasta et al. 2012)</td>
<td>9 healthy nonsmoking male subjects</td>
<td>No significant increase in IOP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 head down Yoga positions(Fig.1)</td>
<td>10 POAG subjects</td>
<td>+16–70% of IOP from baseline</td>
<td></td>
</tr>
<tr>
<td></td>
<td>for 2 mins (Jasien et al. 2015)</td>
<td>10 healthy subjects</td>
<td>+15.1 mmHg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Headstand Yoga posture for 5 mins (Baskaran et al. 2006)</td>
<td>75 subjects</td>
<td>No difference in the two groups</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Headstand yoga posture on a daily basis for years (Gallardo et al. 2006)</td>
<td>A 46-year-old female NTG patient</td>
<td>Progressive optic neuropathy and visual field defects</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Headstand yoga posture 10 mins per session, 3 times per week for years (de Barros et al. 2008)</td>
<td>A 46-year-old female congenital glaucoma patient</td>
<td>+12–15 mmHg, progressive optic neuropathy</td>
<td></td>
</tr>
<tr>
<td><strong>Martin’s vigorimeter</strong></td>
<td>For 90 second (Portmann et al. 2011)</td>
<td>45 healthy subjects</td>
<td>−</td>
<td>OPP: healthy subjects: +11.7%; POAG subjects: +14.0%; OHT subjects: +14.2% ChBF: healthy subjects: +3.7%; POAG subjects: +8.1%; OHT subjects: +5.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>45 POAG subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>45 OHT subjects</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

− = decrease; + = increase; AMD = age-related macular degeneration; BF = blood flow; ChBF = choroid blood flow; CME = continuous moderate exercise; CSC = central serous chorioretinopathy; HIT = high-intensity-interval training; IOP = intraocular pressure; MAP = mean arterial pressure; MVC = maximal voluntary contraction; NTG = normal-tension glaucoma; OBF = ocular blood flow; OHT = ocular hypertension; ONHBF = optic nerve head blood flow; OPP = ocular perfusion pressure; OSA = obstructive sleep apnoea; POAG = primary open-angle glaucoma.
and depression (Mead et al. 2009), most of the researches support the conclusion that exercise is helpful in reducing symptoms of depression or anxiety and serves as a potential treatment for such mental diseases (Barbour & Blumenthal 2005; Harris et al. 2006; Trivedi et al. 2006; Rethorst et al. 2009; Oelend et al. 2010; Rimer et al. 2012; Cooney et al. 2013). The efficacy is dose-dependent (Dunn et al. 2002, 2005). The most commonly used and effective prescription was three times per week of 30-min aerobic exercises at 60–80% of maximum heart rate, and maintaining it for at least up to 8 weeks (Perraton et al. 2010). The underlying mechanisms are complex, including upregulation of adiponectin (Yau et al. 2014) and BDNF in the brain (Dey 1994; Salmon 2001; Zheng et al. 2006; Duman et al. 2008), as well as enhancing the sensitivity of serotonin receptors (Dey 1994). Therefore, in addition to preventing RGC loss via IOP control and increasing ocular perfusion, exercise may be beneficial in enhancing the overall well-being of patients with glaucoma, and thus improving their quality of life.

Conclusion

In 2009, David Risner et al. published a review focusing on the effect of exercise on IOP and OBF. In that review, a consensus was made that both dynamic exercise and isometric exercise could lower IOP, although there were conflicting data suggesting that IOP increased or remained unchanged in certain isometric exercise. To provide the most updated evidence, our current review is conducted on top of the review published in 2009, and all the relevant publications regarding the effect of exercise on IOP and OBF published from 2009 to 2016 were reviewed. In addition, this review also involved some other types of exercise, such as swimming, Yoga and some extreme sports, which have not been discussed in David Risner’s review.

Our review suggested that dynamic exercise is effective in reducing IOP in healthy or myopic subjects, as well as in patients with glaucoma (except in those with PDG or PDS). However, although swimming with goggles is considered safe in the healthy population, it has the potential to elevate the IOP to damaging levels and result in disease progression in patients with glaucoma. Extreme exercises, such as scuba diving and bungee jumping, should be warned in patients with glaucoma due to the potential risks, although more studies are required to support the conclusion. In contrast to the review in 2009, most new evidence during our search revealed that IOP transiently increased during isometric exercise. Furthermore, performing isometric exercise, especially body inversion in Yoga, requires special precaution in patients with glaucoma, because it is known to cause IOP elevation. We suggest that high-intensity exercise involving breath-holding or head-down position, which could cause sudden IOP elevation, should be avoided in these patients. There is no literature available regarding the effects of exercise following glaucoma laser or surgery, where more studies would be warranted.

Physical exercise consistently improves OPP, but the effect on ocular circulation is dampened by autoregulation in healthy subjects. However, more studies are required to evaluate the potential benefit of physical exercise in enhancing OBF in patients with glaucoma, who are known to have an impaired autoregulatory response. With the development of more investigative tools that evaluate OBF, including the optical coherence tomography angiography, we anticipate that the effect of exercise on ocular circulation can be studied in more detail and depth. Current evidence points to a transient impact of exercise on IOP and OBF. Although evidence also suggested a lower baseline IOP in subjects undergoing chronic exercise, how it affects glaucoma control, together with the chronic effect on OBF, which are more important in halting glaucoma progression, would require more supporting evidence.

In addition to IOP and OBF, the effects of exercise on neuroprotection and the mental health in patients with glaucoma were discussed. Upregulation of BDNF and enhancement of mitochondrial function might be effective in preventing vision loss caused by RGC death from glaucoma. Last but not least, anxiety and depression, which are common among patients with glaucoma, can be potentially alleviated with physical exercise, thus improving the quality of life of these patients with chronic disease.

To conclude, this study summarizes the most updated evidences regarding the effects of physical exercise on IOP, ocular perfusion, neuroprotection and the mental health in patients with glaucoma. Although the limitations of a traditional review, such as an unstrict search strategy, non-specific inclusion and exclusion criteria and the bias of results’ interpretation, cannot be totally avoided when performing this study, this review provides a relatively comprehensive, detailed and thorough point of view on this topic. It may give an overall concept to clinicians and support them in the management of their patients when they are entangled with what kind of exercise should be encouraged or avoided in glaucoma.

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Correspondence: Bonnie Nga Kwan Choy, FRCOphthHK Department of Ophthalmology LKS Faculty of Medicine The University of Hong Kong Room 301, Block B, Cyberport 4 Hong Kong SAR, China Email: bonniechoynk@gmail.com