The Glymphatic System – Potential Interventions

There are five main categories when it comes to glymphatic system support. Sleep is the primary intervention for a well-functioning brain waste clearance system. Supporting brain and nervous system health, cognition, detoxification via the lymphatic system and improving circulation also help to maintain an optimal glymphatic system. Symptoms associated with poor glymphatic system function usually revolve around the lack of sleep – with potential accumulation of brain waste. These may include brain fog, neurological and cognitive dysfunction, migraine headaches and some mood disorders.[1-7] In patients requiring support in glymphatic clearance, looking at helping maintain these five categories may be a beneficial treatment strategy.

Sleep Support

Sleep is the primary driver for glymphatic clearance.[8,9] Glymphatic flow and activity is 90% more active during sleep than wakefulness, according to animal research.1,9 The highest rate of glymphatic flow and brain waste clearance is during the deepest sleep stage, non-REM 3 (N3) sleep.[3,10] Increased influx of CSF during N3 sleep has been demonstrated in both animal and human studies.[11]

Certain herbs and nutrients can help support sleep. Lemon balm has been used traditionally to induce sleep and improve sleep quality.[12] In a small study, lemon balm reduced measures of insomnia by 42% overall, including time to fall asleep, restlessness at night and early awakening, with 85% of participants reporting improvements.[13]

Research suggests that phytomelatonin may help support healthy sleep circadian rhythms.[14,15] Maximum secretion of melatonin, the key regulatory hormone for the sleep phase of circadian rhythms, corresponds with the time when the glymphatic system is most active.[16] Therefore, circadian rhythms may influence glymphatic system clearance.[16]

Clinical research has reported that 3 g glycine, taken before bed improves overall sleep quality and sleep efficacy, compared with placebo, especially in those experiencing sleep difficulty.[17-21] The core mechanism by which glycine promotes sleep quality is due to a thermoregulatory action which promotes a drop in core body temperature, corresponding to the commencement of N3 slow wave sleep.[20-23]

Magnesium plays a role in sleep regulation, with low magnesium levels linked to poor sleep quality, low melatonin levels and altered circadian rhythms.[24] Magnesium helps regulate sleep due to NMDA antagonist and GABA agonist actions.[24] In a small clinical study in individuals >60 years, supplemental magnesium significantly improved subjective and objective measures of sleep disturbances.[24] In this study, magnesium also lowered cortisol levels, which contributed to improved sleep quality.[24]

Brain and Nervous System Health

Brain health has an influence on glymphatic system health. There are interventions that can significantly improve brain health and support nervous system function. Raised noradrenaline, a key neurotransmitter in the fight or flight response, impairs the glymphatic system, as it impairs inflow of CSF flow into the brain interstitial space.[9] Preliminary research suggests low GABA levels coincide with glymphatic dysfunction, while increased GABA promotes glymphatic function. This provides an additional mechanism by which to help modulate brain waste clearance.[25,26] Animal research also suggests chronic stress may compromise glymphatic system activity.[27]

Lemon balm has been used traditionally to promote relaxation.[12] Research suggests lemon balm increases GABA levels by inhibiting activity of GABA transaminase (GABA-T), thereby reducing GABA degradation.[28] A small study reported that lemon balm reduced symptoms of mild anxiety by 15%, agitation by 35% and tension by 18%.[13] Lemon balm has also been shown to induce a sense of calmness in other human studies.[12,29,30]

Magnesium is a co-factor nutrient for neurotransmitter synthesis and transmission and helps maintain nervous system function.[31,32] Magnesium protects the integrity and function of the blood-brain barrier (BBB), with evidence suggesting that magnesium helps prevent BBB disruption, reduces hyperpermeability and supports repair.[33-39] Animal research shows magnesium deficiency is linked to low-grade inflammation, including neuroinflammation, which compromises BBB integrity.[35] Magnesium may also be neuroprotective by upregulating antioxidant enzyme activity and inhibiting production of reactive oxygen species (ROS).[35,39]

Research has identified that exercise is beneficial for brain health and helps support cognition in the elderly.[9] Exercise may serve as a neuroprotective lifestyle intervention to support brain health and glymphatic function.[9]

In animal research, exercise has been shown to accelerate glymphatic flow, reduce neuroinflammation by decreasing the activation of astrocytes and microglia, restore brain homeostasis and improve memory and cognition in neurodegenerative disease.[9,40]

Choline is an important component of cell membranes and plays an important role in brain function, neurotransmission and cell membrane signalling.[41-43] Cellular membrane breakdown is a typical feature of neurodegenerative disorders.[44] Choline supplementation appears to downregulate microglial activation in the brain, which may reduce neuroinflammation.[45]

Cognition and Memory Support

Lemon balm has improved cognitive performance and working memory in several studies.[13, 29,30] The findings of a 96-week study conducted in older adults diagnosed with mild cognitive impairment or mild Alzheimer's disease (AD) suggest that lemon balm may help prevent cognitive decline in older adults who do not have hypertension.[46]

Choline is the precursor for acetylcholine, which is an important neurotransmitter for memory, mood and other brain and nervous system functions.[41,47] Preliminary findings suggest that choline supplementation may improve cognitive function in some individuals.[48] Choline appears to increase the density and activity of receptors which play a role in normal cognitive processes including processing speed, attention, working memory and executive function.[48]

Centella has been used in traditional herbal medicine to support brain health and memory.[49] Preliminary animal and laboratory studies suggest centella has neuroprotective properties, reducing inflammation and oxidative stress, which support neuronal health.[50]

Omega-3 fatty acids also have anti-inflammatory properties and modulate amyloid-β aggregation.[9] Epidemiological studies associate increased levels of omega-3 fatty acids with a lower incidence of neurodegenerative disease.[9]

Ginkgo has been shown to improve some parameters of cognitive performance such as working memory, speed of processing and executive function, especially with ongoing use.[51, 52-55] Improved cognition has also been reported with acute use.[56,57]

Lymphatic and Detoxification Support

The glymphatic and lymphatic systems can be seen as a functionally integrated unit.[1,10] Brain waste exits brain tissue via the glymphatic clearance system and ultimately drains into the meningeal lymph vessels.10 Thereafter, the waste is transported via the lymphatic system to the bloodstream and then to the liver or kidneys for degradation and elimination.[1,4] Poor lymphatic system function will therefore influence the efficiency of glymphatic system clearance.[4,10,58]

Calendula *(Calendula officinalis)* has been used in traditional Western herbal medicine to support a healthy lymphatic system, to aid natural detoxification processes and to maintain natural channels of elimination in the body.[59,60] Calendula also demonstrates anti-inflammatory properties.[60]

Circulation Support

Arterial pulsation is a key driver of glymphatic movement and flow of CSF into brain tissue.[10,61,62] Reduced cardiac function and decreased cerebral arterial circulation due to cardiovascular disease or age may diminish glymphatic flow.10 Hypertension may also reduce glymphatic flow due to stiffening of the arterial wall and loss of blood vessel elasticity.[10]

Ginkgo has been shown to increase cerebral blood flow in older adults in a small clinical study.[63] In another 8-month study, ginkgo, improved cerebral perfusion, reduced blood viscosity and improved global cognitive function in older adult men.[51] Ginkgo has been shown to improve vasoregulation and peripheral blood flow microcirculation.[64]

Omega-3 fatty acids derived from fish oil have been found to modulate glymphatic activity. In animal models, supplementation reduced neuroinflammation and led to higher CSF influx and clearance, improved AQP4 function and increased speed of glymphatic clearance.[9,65] Omega-3 fatty acids were shown to help restore glymphatic system disruption and protect cerebral vascular function in mice.[65]

It is also well known that consumption of omega-3 fatty acids in the diet and through supplements promotes cardiac health and lower triglyceride levels, especially in those who have low dietary omega-3 intakes.[66,67]

The glymphatic system is connected to varying systems throughout the body. Supporting these systems, and therefore better-quality sleep, through herbs, nutrients and lifestyle choices, may be the key to healthier brain waste clearance and therefore a healthier mind.

**References available on request.*