Title: Weighting Evidence in MS: Obesity and Neurodegeneration

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Multiple sclerosis (MS) is an immune-mediated, neurodegenerative disorder, characterized by central nervous system (CNS) inflammation.[1] The cause of MS is unknown, and there is no cure. Despite the widespread availability of disease-modifying therapies (DMTs), MS continues to be an important cause of non-traumatic neurologic disability among young adults.[1] Hence, there is a clinical impetus to identify modifiable factors that may ameliorate the risk of MS diagnosis, and disease severity.

Obesity and metabolic syndrome have been linked to more rapid disability progression, and accelerated rates of brain atrophy in people with MS.[2,3] The pathobiological basis of these relationships remains opaque. Various theories have been proposed to explain the correlations between metabolic syndrome, and CNS inflammatory reactions in MS. Specifically, abdominal adiposity has been associated with increased secretion of proinflammatory cytokines, elevated cortisol levels, greater insulin resistance, deleterious effects on the gut microbiome, and increased oxidative stress.[2] In the current issue of the *Multiple Sclerosis Journal*, Filippatou and colleagues[3] explore the retrospective relationship between obesity [represented by body mass index (BMI)], and retinal neuroaxonal loss [measured by optical coherence tomography (OCT)] in 513 MS patients. At "baseline" participants were categorized as being of "normal weight" (BMI = 18.5 to 24.9 kg/m^2), "overweight" (25.0 to 29.9 kg/m^2), or "obese" ($\geq$ 30 kg/m^2). The OCT measures included the peripapillary retinal nerve fiber layer (pRNFL) and the macular ganglion-cell-inner plexiform layer (mGCIPL) thicknesses. Obesity was associated with accelerated mGCIPL atrophy [-0.57% (CI:-0.65% to - 0.48%) compared to normal body weight [-0.42% (-0.49 to -0.35%; p = 0.012)]. For each 1kg/m^2 BMI increase, the mGCIPL thickness decreased by -0.011%/year (95% CI: -0.019% to -0.004%; p = 0.003). The authors conclude that obesity may be associated with increased rates of retinal neuroaxonal loss, as a marker of neurodegeneration in MS.

The strengths of this study include the fact that actual BMIs were measured in a multi-ethnic cohort, and a rigorous statistical approach. The retrospective nature of the study,

decreased likelihood of DMT use among obese patients, and absence of detailed ophthalmic examinations are among its limitations. Notably, glaucoma, diabetic retinopathy, and hypertensive retinopathy have ethnicity dependent prevalence figures, and cause atrophy of the pRNFL and mGCIPL. Blood pressures, intraocular pressures (IOPs), serum glucose levels, and lipid values were not systematically evaluated. These variables may impact pRNFL and mGCIPL measures, and also co-associate with metabolic syndrome. [4-6] The effect size of BMI on mGCIPL thinning in this study was modest, and functional outcomes were lacking, making it uncertain whether the retinal changes were specific for MS and had clinically-meaningful consequences.

The most significant shortcoming in this study is the lack of a control group, particularly since obesity is associated with lower pRNFL and mGCIPL measures, independent of MS diagnosis. [7-8] In a British twins study involving 1657 participants, inner retinal thinning was associated with increased age and elevated BMI. For every 1-unit increase in age or BMI , there was a decrease of the macular ganglion cell complex (mGCC) thickness by 0.14-microns (μm) and 0.15-μm, respectively.[7] The recently published UK Biobank study examined the epidemiologic features of macular inner retinal anatomic characteristics in 42 044 participants .[8] Again, a higher BMI was significantly associated with mGCIPL thinning; per 1 kg/m2 BMI increase, the mGCIPL thickness

decreased by -0.035% (95%CI -0.046, -0.024, p=7.1 x 10 -1). Other factors related to lower mRNFL, mGCC, and mGCIPL measures were age, male gender and non-Caucasian ethnicity. [8] The thinner mGCC thickness seen in blacks compared with

whites in the UK Biobank Study had a magnitude of 26% of the standard deviation of this measure, equivalent to being 10 years older. [8] Inner retinal measures were also significantly lower in participants with greater alcohol intake, more social deprivation, and lower educational attainment.[8] The strongest association observed was between mGCIPL thinning and IOP elevation, highlighting the relevance of excluding glaucoma. With reference to the study by Filippatou and colleagues,[3] it should be noted that ocular hypertension, and primary open angle glaucoma are conditions five times more likely to affect African Americans than Caucasians; [9] which may have impacted their results since African Americans made up a third of their obese cohort.

Akin to the relationship between obesity and neurodegeneration, inflammatory mechanisms have been implicated in the link between obesity and retinal neuroaxonal atrophy. Systemic inflammation associated with visceral fat accumulation and reduced lipoprotein lipase activity may increase oxidative stress, leading to retinal degeneration. [4-6] Furthermore, chronic inflammation affecting the trabecular meshwork has been debated as a possible cause of impaired aqueous humour outflow in the eye; [6] the consequent rise in IOP may, in turn, cause retinal neuroaxonal injury. Yet, these pathobiological theories remain speculative, and statistical correlations must not be confused with causality. For example, increased BMI also linearly correlates with elevations in cerebrospinal fluid (CSF) pressure,[10] which over time could have detrimental effects on retinal neuroaxonal structure. Moreover, vascular factors associated with metabolic syndrome may cause ischemic CNS injury. Certainly,

deciphering how obesity and metabolic syndrome might accelerate neurodegeneration in the brain and retina represents an intriguing avenue for future investigation.

The authors of this paper should be commended taking a novel approach to investigate a relevant topic, namely the association between obesity and retinal neuroaxonal atrophy in MS. This study highlights the utility of pRNFL and mGCIPL as outcome measures, but also illustrates the importance of addressing confounders known to affect these OCT parameters. The findings of this study are thought provoking; yet, it is also important to keep in mind that neuroaxonal injury and progressive disability in MS patients may be exacerbated by factors linked to metabolic syndrome, that are independent of disease pathobiology. Weighting the effects of obesity and determining the potential therapeutic benefits of weight loss strategies have important implications for people living with MS and require further study.

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