CJNM
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Table of Contents

Publisher's Letter

I am very excited to announce the launch of the CJNM (Canadian Journal of Naturopathic Medicine). It has been my passion and mission to encourage education and growth of integrative medicine practices for over two decades. As the Founder and President of the Nature's Source and Nature's Signature chains of natural health product dispensaries, I quickly realized the knowledge and skill of naturopathic doctors (NDs) are critical drivers of our industry. I am grateful to partner with the Nutritional Fundamentals for Health Inc (NFH) team and our Editor-in-Chief Philip Rouchotas to create a resource that will help NDs and healthcare providers of all disciplines improve outcomes for their patients.

Years of attending conferences across Canada and the US have introduced me and the NFH team to healthcare providers of all disciplines who have expressed a desire to receive high-quality peer-reviewed academic information focused on integrative healthcare. You may have received an invitation to view the CJNM due to having expressed such interest. If you wish to no longer receive updates from CJNM, please send an email to the address below informing our team of your decision.

As the natural health products industry grows in demand, with constant expansion of new product offerings, so does the need to inform and educate the healthcare providers responsible for the safe and effective use of these substances. Having leading healthcare providers from across Canada, North America, and beyond compile their protocols and monographs to share with their peers delivers on an ongoing personal mission I have held for years; giving doctors tools to help them be great at what they do.

We look forward to your feedback on helping us in helping you!

Sanj

Sanjiv Jagota
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Editor's Letter

It is humbling and exciting to be invited to serve as the Editor-in-Chief of the newly launched Canadian Journal of Naturopathic Medicine (CJNM).

The CJNM has been created to provide a compilation of evidence-based reviews of clinical importance authored by leading members of the profession, coupled with a rigorous single-blind process of peer review, delivering tools that are indispensable to practicing naturopathic doctors (NDs), and other healthcare providers across all disciplines of medicine. As the Journal matures, we expect to also feature human intervention trials addressing topics of interest to integrative healthcare providers.

This project has been made possible by the never-relenting commitment of members of the profession to drive the practice of naturopathic medicine in a forward direction.

CJNM is a not-for-profit initiative philanthropically created by the generous support of Nutritional Fundamentals for Health Inc (NFH). NFH endeavours to help NDs elevate their profession, and in doing so delivers valuable tools for healthcare providers such as CJNM as well as Nutramedica.org, reaching clinicians of all disciplines. I am also excited to once again partner with Sanjiv Jagota of Nature's Source who has welcomed the opportunity to serve as Publisher for this important project.

A big thank you to David Schleich for an inspiring commentary in this inaugural edition to help launch this important project. I found it very inspiring. It made me reflect on a phenomenon I have observed over years of practice. In the early days, rheumatologists would be critical of patients I was working with that implemented gluten free/dairy free diets. A handful of years ago I recommended such a diet to a patient newly diagnosed with rheumatoid arthritis. The patient replied "my rheumatologist told me that might help". Evidence-based interventions that are safe and deliver important magnitudes of efficacy will always see the light of day, regardless of obstacles that may hinder their widespread acceptance.

I am extremely pleased with the line up of articles contained within this first volume of CJNM. Eric Muradov delivers a thesis on preclinical and human evidence in relation to strategies that encourage remyelination for individuals suffering from MS. Neil McKinney provides a thorough review of a novel natural health product most specific for pain management; palmatoylethanolamide (PEA). Erin Balodis updates happenings in relation to the FODMAPs diet. Jenny Henderson and Elizabeth Goldspink deliver a powerful summary of evidence regarding benefit of spending time in greenspaces. Maria Shapoval reminds us to "use it or lose it" as she reviews evidence of cognitive benefit of video games among the elderly. Gillian Flower does an excellent job of examining the potential role of metformin as a treatment for non-diabetic patients suffering with cancer.

On behalf of the editorial group and sponsors here at CJNM, it is my hope that you will find this publication useful in advancing your profession and practice. Please do not hesitate to submit your best work for consideration for publication in our community's newest information dissemination resource.

Philip

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CJNM would like to thank the following individuals for their efforts in serving as Referees, undertaking the process of Peer Review for this issue of the Journal.

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Canadian Journal of Naturopathic Medicine

The Pillars of Professional Formation Just Got Stronger

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Invited Commentary
The Pillars of Professional Formation Just Got Stronger

When I reflect on the steady drift from reductionist approaches in health care toward more holistic, patient-centered models, I'm reminded that there are two imperatives afoot here. On the one hand, there is the dominant mainstream health system experiencing uncertainty about persisting hegemony. On the other hand, there is the certitude of naturopathic medicine burdened by a defensiveness in the face of huge numerical, political and economic odds.

Andre Gide's phrase, "contrary imperatives" is at work here in the dynamics of professional formation for naturopathic medicine. Let's have a look at a painting to help us decode this conundrum.

There is a small oak panel painting in the National Gallery in London, UK, about the crucifixion of Christ which illustrates among other things the elements of the four humours which shaped medicine and science at the end of the fifteenth century. Among the National Gallery's fabulous collection Hieronymus Bosch's *Christ Crowned With Thorns* is a seminal work in the Christian tradition. It is an ageless allegory embedded in an unconventional portrayal of four tormentors in the story of Christ's crucifixion. The work captures the essence of our present place in the evolution of contemporary naturopathic medicine. The idea is that even though our detractors persist, our response is confident and strengthening. There is underlying idea operating here, though, that the confident certitude of our detractors is not consistent.

The stunning figures in Bosch's painting are enigmatic in their depiction of a complex event in the evolution of western culture at the painful, political and urgent advent of a major new religion. The figure at the lower right of the painting, persistently yanking and pulling at Jesus' cloak is uncertain in his actions. Bosch portrays him with a partly confident certitude coupled with determination, a rendering which conveys fragility at the edge of transformation. The advantage and power of the tormentors is not assured.

What *is* the torment aimed at heterodox medical professions all about, anyway? It is about the migration away from reductionist medicine toward a reluctant collaboration. It is about philosophy and results. Informing that whole dynamic are data, though, grounded in the growing research presence of naturopathic medicine in global health care.

A kind of fluctuating but *confident certitude* has been part of our landscape for a while now as we build the key pillars of professional formation in naturopathic, functional and integrative medical practice. Even so, today's health care professionals worry about where this more integrated, person-centered health practice is headed. What will this new angle on the design and

delivery of health disrupt? Natural medicine providers may be concerned that they are not holding on to enough purchase on the tricky terrain of an erratic post-Covid terrain. All around are scurrying practitioners, suppliers, patients, policy makers and scholars. There is ample reason to shake off that worry.

We can rely on the three key pillars of professional formation to sustain momentum: *social closure (naturopathic medicine is gaining legitimacy), third party accreditation (our credentials are increasingly recognized)* and *the codification of the knowledge of the profession* is accelerating, showing up in the literature, policies and regulatory frameworks of the land. This latter pillar, codification, is anchored in research and teaching.

There are now twenty-two American States and five Canadian provinces licensing naturopathic doctors in North America. Just recently Tina Hauser (Europe) and Jill Dunn (New Zealand) and colleagues documented the growing panoply of professional naturopathic education programs in place globally. The new World Naturopathic Federation, led by Dr. Iva Lloyd (Canada) has a strong presence within the World Health Organization, and is very busy organizing, researching and lobbying. The ICNM (International Congress on Naturopathic Medicine) will offer its sixth international conference in 2022 in Paris, with a poignant focus on research, poised to welcome upwards of 750 delegates from sixty countries.

However, this dynamic means that the floodwaters of accountability, flexibility, diversity, access and competition require data to guide leaders through the turbulence ahead. Naturopathic leaders and civil policy makers alike need robust and expanding research. Sharing that work and helping with the burden of professional formation are fundamental to the purpose of the new *Canadian Journal of Naturopathic Medicine*.

This new journal fits beautifully into the naturopathic profession's enduring commitment to systematically establishing a theory of naturopathic medical knowledge, and to articulating in an ongoing way its methods and validation.

Of interest as we think about an epistemology of naturopathic medicine is that one of its parts, biomedical knowledge, is *theoretical* too, in that it comprises the knowledge and research conjugated through fields such as human and veterinary medicine, odontology, as well as the fundamental biosciences including biochemistry, biology, chemistry, embryology, histology, genetics, pathology, microbiology and botanics.

The historical record, however, demonstrates that biomedicine has been less concerned about the whole of its nature being greater than the sum of its parts, proud as it is of the dominance of scientific method. Biomedicine appears often to concentrate more on the theory, knowledge and research of medicine, than on the actual practice of medicine, and simply assumes that its philosophical underpinnings are substantial enough to carry the day. Biomedical doctors feel confident that they are properly grounded in effective, safe, surgical technique, always at work

introducing new drugs, and assured epistemologically and clinically that their deeper, molecular understanding of the mechanisms underlying disease is the way to go.

As our presence clinically and in broad research gains ground, our allopathic colleagues are noticing that they are less able to insist unilaterally that biomedicine alone guards the foundation of all medical application, diagnosis and treatment. Baer (2001) has said that biomedicine is a “dominative” system, orthodox in its location in civil society and that naturopathic medicine is “heterodox”. They are all, Baer says, “medical systems” and the proper subjects of medical history and of theories of knowledge.

There are other parallel academic conversations which give us insights into the foundations and futures of such medical systems. For example, some social scientists and medical historians have examined theories of knowledge which underlie the medical professions and basic medical science disciplines; increasingly they challenge some of the assumptions and certitudes which those systems claim. Power (2000), for example, asserts, "Rarely questioned [is] the idea of science as essential to medicine.” Wetzler’s work (1984) is telling in this regard. As well, contemporaries of Wetzler such as Nixon (1984) explain that challenging the dominance of the epistemological bases of biomedicine constitutes a 'paradigmatic shift' from reductionism to "an integrative, humanistic or holistic approach." Leavell and Clark (1965) much earlier focused on their widely circulated model of prevention as an interpretation of the natural history of disease process. Their model's intensity gradient (sub-clinical/unapparent disease; diagnosis; death) were very familiar to the ND and to the MD. In academic medicine competing clinical delivery systems and intersecting philosophies need new inquiry to help us through. Social-scientific debate can only be enriched by good, protracted research.

Naturopathic doctors have long launched every healing journey focused on primary prevention, i.e. making people more resistant to infection and slowing the progress of a particular disease via education, supplements and mind/body alignment techniques such as meditation and stress reduction. In contrast, the allopathic world’s pharmaceutical industry has most often developed medications based on empirical observations, and more recently, on known disease mechanisms. The biomedicine health professional has routinely articulated his or her understanding of what to do, say with antibiotics, on the observation that microbes produce substances that inhibit other species.

Whether it is her approach to establishing treatments for high cholesterol by creating medications which target the absorption, metabolism and generation of cholesterol, or the technique of treating diabetes by improving insulin release, the allopathic doctor’s medications illustrate an epistemological underpinning based on mechanisms of disease, the understanding of which mechanisms emerged from bench science as much as from observing and treating patients. These days, and somewhat ironically some would insist, the very personalized nature of naturopathic medicine is increasingly mimicked by allopathic practitioners as nutrition takes centre stage in functional medicine clinics or cutting-edge genetics research accumulates in the lexicon. In both

these cases, customized care so familiar to naturopathic doctors becomes more scientifically accepted. Thus, the work ahead for the *Canadian Journal of Naturopathic Medicine* is big in terms of its mission to add to this literature and to encourage inter-professional collaboration.

Despite tugging figures and fluctuating certainties all around, these research professionals and the dozens more in training now have yet another substantial place to publish their work and publish they will.

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Alternative Approaches to Remyelination in Multiple Sclerosis

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Conflict of Interest

The Author declares no conflicts of interest.

Alternative Approaches to Remyelination in Multiple Sclerosis

Abstract

There are no currently approved remyelination therapies for Multiple Sclerosis (MS). However, understanding the composition of myelin, nutritional contributors towards myelination as well as non nutritional alternative approaches may aid those in need while other methods are developed. Fatty acids, vitamins and minerals are needed at different points in the biochemistry of myelination. Furthermore, repurposed medications, peptides, lifestyle interventions and amino acids also may be of benefit. Lastly, it appears that a synergistic approach may be more effective than pharmacologic dosing of individual nutrients.

Background

Multiple sclerosis (MS) is typically a relapsing, inflammatory condition of the central nervous system (CNS) (Tryfonos et al 2019). In Relapsing Remitting MS (RRMS) lymphocytic infiltration of the brain and spinal cord dominates early on, causing demyelination (Baldassari and Fox 2018). Oligodendrocytes are involved in the formation of myelin in the CNS (Dietz et al 2016). Oligodendrocytes also provide nutrition to the axons, fuelling axonal mitochondria, and support energy-demanding axonal transmission (Lubetzki et al 2020). Understandably, oligodendrocytes require two to three times more energy other brain cell types (Weiser et al 2016). Oligodendroglial loss and axonal injury also occurs as result of the lymphocytic processes (Kremer et al 2019). Local processes within the CNS are also thought to drive the disease which include localized inflammation driven by microglia and B-cells and resulting neurodegeneration, particularly in progressive MS (Faissner et al 2019).

The myelin sheath is interrupted by nodes of Ranvier so the action potential jumps from one node to the next (saltatory conduction) which allows rapid transmission of the action potential along the axon which is up to 100 times faster than unmyelinated axons (Monje 2018). The loss of myelin therefore leads to slower transmission of the action potential and contributes to the focal neurological clinical abnormalities common to the disease. The oligodendroglial loss leads to a loss of axonal nutritional support for ATP production contributing to eventual axonal loss (Cunniffe and Coles 2021). Demyelination increases the number of Na+ channels along the length of the axon which elevates the energy demands on the axon (increased Na+/K+ ATPase activity for axonal polarization, which in turn is needed for transmission of action potentials). If the energy demands are insufficiently met, the axonal Na+ gradient diminishes and the Na+/Ca2+ exchanger reverses and causes toxic levels of Ca+ in the axon and axonal degeneration ensues (Friese et al 2014). Therefore, remyelination is important not only to improve neuronal function and therefore clinical symptoms but also to prevent subsequent axonal loss and resultant neurodegeneration.

While spontaneous remyelination can occur, it is often incomplete. Remyelination is variable with some patients having extensive remyelination while others have almost no evidence of neuronal repair (Wooliscroft et al 2019). Myelin repair in the adult CNS appears to depend on pre-existing mature oligodendrocytes (Yeung et al 2014). Oligodendrocytes in the adult CNS are post-mitotic and are unable to proliferate and replace damaged oligodendrocytes (Zhang et al 2016). Pre-existing mature oligodendrocytes are able to increase their neuronal internodes and therefore contribute to recovery after demyelination (Duncan et al 2018). Experimental models in particular have established that after demyelination, new myelin can be synthesised by newly formed oligodendrocytes generated from oligodendrocyte precursor cells (OPCs) or neural stem cells (Lubetzki et al 2020). Rate of oligodendrocyte production decreases after five years of age and subsequently occurs at low levels. Remyelination is greatest in people aged less than 55 years and within the first 10 years of disease onset (Plemel et al 2017). Impaired recruitment of OPCs into a lesion and inability to differentiate into mature remyelinating oligodendrocytes are two main factors contributing to remyelination failure, with the latter a strong area of focus with regards to regenerative myelination approaches (Dulamea 2017). One study found that 20% of patients with MS repaired plaques efficiently (between 60% and 96% remyelinated) (Patrikios et al 2006). Optimistically, this suggests that close to full myelination is possible and perhaps there are modifiable factors that contribute towards it. This paper will explore lifestyle, hormonal and nutritional contributors in addition to easily accessible nutraceuticals and medications to potentially encourage the process.

Myelin composition: Myelin consists of 40 or more tightly wrapped lipid bilayers, and is 70-85% lipid and 15-30% protein in composition (Poitelon et al 2020). Structural proteins inside of myelin include Proteolipid Protein which accounts for over half the total protein in CNS myelin and Myelin Basic Protein that accounts for about 30% of the total in CNS myelin. A final major myelin protein is Myelin-Oligodendrocyte Glycoprotein, which is specific for the CNS and is selectively localized on the outside surface of myelin sheaths and oligodendrocytes and is susceptible to autoimmune attack (Quarles 2005).

The three classes of membrane lipids are cholesterol, phospholipids and glycolipids in a ratio of 40%:40%:20% respectively (Poitelon et al 2020). The brain contains about 20% of the body's cholesterol, and due to the blood–brain barrier (BBB) the cholesterol present in myelin mostly comes from de novo synthesis in oligodendrocytes (Dietschy and Turley 2004).

In terms of glycolipids, the two sphingosine-containing glycolipids, the glycosphingolipids-galactosylceramide (cerebroside) and sulfatide (the sulfated form) are the most common lipids in myelin. Through transfer of sugar moieties to ceramide, galactosylceramide and glucosylceramide are generated, which can be further transformed into ganglioside and sulfatide, and are required for the stability and maintenance of myelin into old age (Schmitt et al 2015). Sphingomyelin is a phospholipid that is another major myelin component with a sphingosine backbone also produced from ceramide.

Plasmalogens are phospholipids, and are the next most abundant lipids present as phosphatidylcholine (PC) and mostly phosphatidylethanolamine (PE) species (a choline or ethanolamine head group) which can then produce phosphatidylserine. Phosphatidylcholine and ceramide are precursors for the synthesis of sphingomyelin (Denisova and Booth 2005, Vos et al 1997). In the *sn*-1 and *sn*-2 positions of their glycerol backbone, plasmalogens contain a fatty acyl chains, which is usually a polyunsaturated fatty acid, typically docosahexaenoic acid (DHA) in the *sn*-2, and a saturated fatty acid, typically arachidonic acid (AA) in the *sn*-1 position (Manni et al 2018, Paul et al 2019).

Oligodendrocytes require access to large quantities of lipids to myelinate multiple axons but to what extent this demand is supported by endogenous synthesis or lipid uptake is not fully understood (Dimas et al 2019). The brain is capable of synthesizing only a few nonessential fatty acids, therefore both essential fatty acids and even some nonessential fatty acids must enter the brain from the blood as free fatty acids through the blood brain barrier (Mitchell and Hatch 2011).

Nutritional Approaches

Humans can synthesize saturated and monounsaturated fatty acids, but they are not able to synthesize the n-3 fatty acid alpha-linolenic acid (ALA) and the n-6 fatty acid linoleic acid (LA) (Janssen and Kiliaan 2014). Downstream of ALA, quantitatively DHA (22:6n-3) makes up over 90% of the n-3 polyunsaturated fatty acids (PUFAs) in the brain as both eicosapentaenoic acid (EPA; 20:5n-3) and alpha-linolenic acid (ALA; 18:3n-3) are in the brain in only very small quantities. EPA conversion is not a significant source of DHA (Weiser et al 2016). It is well known that EPA and DHA can help control the magnitude and duration of inflammation by modulating innate and adaptive immune responses, thought of as “the fire fighters that extinguish inflammation” (Zahoor and Giri 2021). Beyond the 3-series of prostaglandins, and the 5-series of leukotrienes, EPA converts to specialized pro-resolving mediators (SPMs) namely the E-series resolvins and DHA to the D-series resolvins, protectins (known as neuroprotectins in neural tissues), and maresin SPMs (Duvall and Levy 2016). Also, n-3 PUFAs can help shift microglial polarization toward the beneficial M2 phenotype both in vitro and in vivo (Chen et al 2014). Clearly, beyond regulating inflammation, n-3 PUFAs have potential with regards to myelination because of their role in the structure of myelin phospholipids. Furthermore, DHA promotes oligodendrocyte progenitor maturation and counteracts the maturational arrest induced by TNF-α (Bernardo et al 2017). DHA has been shown to induce BDNF (brain-derived neurotrophic factor) expression both in vivo and in vitro (Sun et al 2018). BDNF is a neurotrophin and studies have demonstrated that mature oligodendrocytes are responsive to BDNF activity and BDNF directly promotes myelination through its effects on oligodendrocytes (Khorshid Ahmad et al 2016).

With regard to human data, one trial with fifty RRMS patients were administered 4 g/day of fish oil (0.8 g EPA, 1.6 g DHA total) for 12 months versus placebo. Fish oil decreased the serum levels of TNFα, IL-1β, IL-6, and nitric oxide metabolites compared with placebo group, however

there was no difference in expanded disability status scale (EDSS), that is, a DHA dominant fish oil preparation did not improve disability as a standalone treatment, nor did it affect the annualized relapses rate (Ramirez-Ramirez et al 2013).

Comparatively, however, a one-year long double-blind trial where a "Fish Oil" group received 1.98g EPA and 1.32g DHA and a low-fat diet (15% fat) and an "Olive Oil" group received olive oil with the American Heart Association (AHA) Step I diet (30% fat). Outcomes demonstrated a trend towards an increase (worsening) in EDSS (+0.35 EDSS points) in the olive oil group vs. a modest decrease in EDSS (-0.07) in the Fish Oil group (Weinstock-Guttman et al 2005). This suggests that possibly the dose in Ramirez-Ramirez and colleagues (2013) was too low and/or the effect of the fish oil was potentiated by the low-fat diet. Similarly, sixteen newly diagnosed MS patients given fish oil (0.4g EPA and 0.5g DHA), low saturated fat intake recommendations and a low dose B Complex had a significant reduction in annual exacerbation rate and EDSS (-0.54) (Nordvik et al 2000). These findings suggest that modifying dietary fat sources with consideration of the addition of B Vitamins can improve the EDSS, possibly through enhancing myelination. This was done in newly diagnosed MS patients which may also have a greater propensity for repair when less damage is present.

Thiamine (B1), as thiamin pyrophosphate, is a cofactor for the pyruvate dehydrogenase complex, used to convert pyruvate to acetyl-CoA, for use in the Krebs Cycle and therefore can help with neuronal energetics (Kerns and Gutierrez 2017). Thiamine is thought to participate in myelin production as deficiency in rats dramatically reduces brain cerebroside content, which as discussed, is a major component of myelin (Trostler et al 1977). Interestingly, beyond its use for myelination, strong data supports the use of B1 for MS fatigue where 600–1500mg/day orally (dose adjusted for body weight) or 100mg once a week parenterally (in patients larger than 80kg to reduce pill count) was found to improve the Fatigue Severity Scale an average of 41% (Costantini et al 2013). Oral Sulbutiamine (synthetic lipophilic B1) at 400mg has also been studied with positive effects on MS fatigue when taken for two months (Sevim et al 2017).

Riboflavin (B2) is involved in myelin formation in nerve cells, and it is a precursor to Flavin Adenine Dinucleotide (FAD). Riboflavin deficiency is thought to result in impaired brain lipid metabolism as a reduction in the proportion of myelin lipids (such as sphingomyelin, and phosphatidylethanolamine) has been reported in riboflavin-deficient rats (Ogunleye and Odutuga 1989). However, modest riboflavin supplementation (10mg) daily for six months did not alter EDSS scores in RRMS (Naghashpour et al 2013). The dosing in the study was possibly too conservative, for example, in the area of migraine prophylaxis, riboflavin dosing is often 400mg daily (Marashly and Bohlega 2017). Mechanistically, because riboflavin should improve neuronal energetics via FAD, and has a role to play in myelination, supplementary incorporation is suggested.

Vitamin B_3 occurs naturally in two forms: niacin (also called nicotinic acid) and niacinamide/nicotinamide (Gasperi et al 2019). Some preliminary data exists supporting

niacinamide in preventing axonal degeneration, likely through increased NAD+ levels (Kaneko et al 2006). Niacin has been recently found to upregulate CD36 expression and myelin debris clearance in lesions by macrophages and microglia which is then accompanied by enhancement of oligodendrocyte progenitor cell numbers and by improved remyelination in demyelinated mice. Myelin debris contains inhibitors of OPC differentiation and so its clearance, by phagocytosis, is an important step in the regeneration of the myelin sheath (Robinson and Miller 1999). Niacin dosing has not been studied in MS per se, but some older data suggests that the use of high dose oral Niacin (100mg to 3000mg) with other nutrients may be helpful for reversing symptoms in MS (Klenner 1973).

Pantothenic Acid (B5), the precursor of CoA, is an indispensable cofactor especially in the Krebs Cycle (Kelly 2011). CoA plays specialized roles in the brain as Acetyl-CoA Carboxylase (ACC) catalyzes the first committed step in fatty acid biosynthesis which converts acetyl-CoA to malonyl-CoA where it mediates the synthesis of the complex fatty-acyl chains of glycosphingolipids and phospholipids (Ismail et al 2020, Manni et al 2018, Tansey and Cammer 1988). CoA is also needed for cholesterol synthesis beginning with the condensation of two acetyl-CoA molecules to form acetoacetyl-CoA (Cerqueira et al 2016, Czumaj et al 2020). Although B5 has not been specifically studied in MS, its role in cholesterol, glycolipid and phospholipid synthesis implies its appreciable inclusion into the diet of an MS patient.

Vitamin B6, in its coenzyme form, pyridoxal 5′-phosphate serves as a cofactor in sphingolipid synthesis and is thereby important for myelin formation. Pyridoxal phosphate is a cofactor for serine palmitoyltransferase (Denisova and Booth 2005). All sphingolipids share a defining structural component called a long-chain base which are formed by serine palmitoyltransferase in the first and rate-limiting step of sphingolipid de novo synthesis (Lone et al 2020). Furthermore, because synthesis of neurotransmitters like dopamine, serotonin and gamma-aminobutyric acid (GABA) from glutamate depends on pyridoxine, it is also thought to be related to general health of the nervous system and modulating glutamate excitotoxicity (Calderón-Ospina and Nava-Mesa 2020).

Folate (B9) is a generic term for a family of compounds which includes and principally refers to the metabolically active 5-methyltetrahydrofolate (5-MTHF). 5-MTHF is the most abundant form found in plasma, representing more than 90% of folate (Scaglione and Panzavolta 2014). Folate enhances oligodendrocyte maturation both in vitro and in vivo, related to oligodendrocyte-specific dihydrofolate reductase (DHFR) expression as pharmacological inhibition of DHFR causes severe defects in oligodendrocyte survival (Weng et al 2017).

Cobalamin (B12) refers primarily to its principal coenzyme forms Adenosylcobalamin and Methylcobalamin which are for mitochondrial and methylation functions, respectively, both of which impact myelin synthesis (Smith et al 2018). The neurologic manifestations of cobalamin deficiency begin with demyelination, followed by axonal degeneration and eventual irreversible damage due to axonal death in both the CNS and peripheral nervous system (Miller et al 2005).

Adenosylcobalamin is required for Krebs cycle conversion of methylmalonyl-CoA (which is produced from propionyl-CoA) to succinyl-CoA by methylmalonyl-CoA mutase (Froese et al 2019). Cobalamin deficiency results in accumulation of propionyl-CoA which is the launching point for odd-chain fatty acid synthesis, therefore, large amounts of odd-chain (C15 and C17) fatty acids are produced and incorporated into the nerve sheaths, which results in altered, abnormal myelin (Dror and Allen 2008, Metz 1992, Park et al 2020). Methylcobalamin is involved in the conversion of homocysteine to methionine (coenzyme for methionine synthase) which is subsequently converted into S-adenosylmethionine (SAMe) (Froese et al 2019). SAMe is the methyl donor for the conversion of phosphatidylethanolamine to phosphatidylcholine and these lipids account for about 14% and 11%, respectively, of CNS myelin and inefficient conversion may impair myelination or cause demyelination (Dror and Allen 2008). The reaction involves the transfer of a methyl group from 5-MTHF to homocysteine, therefore another role regarding folate's involvement in myelination as well (Scott 1999).

Methylcobalamin given at 60mg orally every day for six months to six patients with progressive MS did not improve motor disability but improved abnormalities in both the visual and brainstem auditory evoked potentials (Kira et al 1994). MS patients given 1mg of Methylcobalamin weekly for six months did result in improvements on a neurological disability scale (Loder et al 2002). Given this information, intake of at least 1mg of methyl-B12 per week is reasonable for a patient with MS.

A more sensitive proposed method of screening for Cobalamin deficiency is the measurement of methylmalonic acid and homocysteine blood levels, which are increased early in vitamin B12 deficiency (Miller et al 2005). Data has suggested that elevated homocysteine, and depressed vitamin B12 and folate serum levels may be associated with MS but historically findings are not always consistent. However, a 2020 meta-analysis found elevated homocysteine in RRMS only, with no differences in serum B12 or folate from looking at 21 studies with 1738 MS patients and 1424 controls (Li et al 2020). However, lower median cerebrospinal fluid vitamin B12 concentrations were found in groups of patients with MS compared to serum levels, yet this was not found with regards to folate concentrations (Nijst et al 1990). MS patients with hyperhomocysteinemia have shown higher disease progression evaluated by the Multiple Sclerosis Severity Score and EDSS. Hyperhomocysteinemia may reflect issues with methylation and hypomethylation of myelin basic protein (a major component of CNS myelin) can destabilize the structure of myelin, and may hinder remyelination or myelin repair (Dardiotis et al 2017). Inborn errors involving the genes of the methyl transfer pathway are known to cause inadequate myelination and serious disability from childhood (Van Rensburg et al 2006).

Pharmacologic dosing of biotin (B7) has recently gained notoriety as a treatment for myelination in MS and has been studied extensively. Biotin serves as a coenzyme for biotin dependant carboxylases that facilitate the transfer of a carboxyl (COOH) group to substrates (Zempleni et al 2009). Acetyl-CoA carboxylase produces malonyl-CoA from acetyl-CoA and citrate. The synthesis of malonyl-CoA represents the rate-limiting step of long-chain fatty acid synthesis in

oligodendrocytes for use in myelin production, as malonyl-CoA is two-carbon building block for fatty acid synthesis. Most studies regarding biotin used 300mg daily, which is 10,000-fold higher than the Adequate Intake (AI) recommended. Therefore, serious exploration regarding the efficacy of its data is warranted (Sedel et al 2016).

A pilot trial administered 100mg to 600mg/day of biotin (with a median of 300mg/day divided in three doses) in 23 primary and secondary progressive MS patients for two to 36 months (mean duration of 9.2 months). Five patients with chronic visual loss had improvement of visual acuity after a delay of two to three months. Sixteen of eighteen patients with prominent involvement of the spinal cord (with tetra and paraparesis) displayed clinical improvement after a two to eight-month delay. Two patients did not respond at all. The EDSS score significantly improved in 4/23 patients (22%) and Timed 25 Foot Walk (TW25) improved in 5/7 cases with paraparesis. Four patients experienced at least one MS relapse but it was suggested the frequency was similar to that observed before treatment in these patients (Sedel et al 2015).

A follow-up study (MS-SPI trial) used 300mg/day (three 100mg doses per day) “MD1003” versus placebo in 154 patients with progressive MS (103 received biotin and 51 received placebo) for 12 months. A total of 13 (12.6%) biotin treated patients achieved reduced disability at month nine, confirmed at month 12 (mean EDSS decreased slightly from baseline) versus none of the placebo-treated patients (EDSS increased at the expected rate). MRI found new lesions in 23.4% of biotin-treated patients and 13.0% placebo-treated patients possibly raising the concern of increased disease activity (Tourbah et al 2016).

Another study by the same investigator, used the same dosing strategy in a six-month, randomized, double-blind, placebo-controlled study with a six-month open-label extension phase, in adult patients with MS-related chronic visual loss. Ninety-three patients received biotin (45 of which had RRMS, and 20 with Progressive MS) and 28 received placebo. At six months, there was an improvement in visual acuity in the biotin group relative to placebo but difference between arms was not significant. The incidence of MS relapse was higher in the biotin group (13.8%) than in the placebo group (3.6%) during the double-blind phase of the study, raising the concern again that high dose biotin might actually increase disease activity (Tourbah et al 2018).

An observational study was published describing 178 progressive multiple sclerosis patients who started high-dose biotin at two hospitals over an approximate 27-month period. At 12 months, 3.8% of the patients had an improved EDSS score. However, 47.4% of the patients described stability, 27.6% felt an improvement and 25% described a worsening (Couloume et al 2020).

In another observational study, 43 patients with progressive multiple sclerosis were prescribed a single daily dose of 300mg of biotin for one year with only 56% completing that period. Twenty-six patients had secondary progressive MS, seven patients had primary progressive MS, ten patients had RRMS. None of the patients' EDSS scores improved and one-third of patients worsened. These authors were concerned that biotin-induced increases in energy metabolism in

diseased axons, along with lack of access to other necessary energy metabolites, may have resulted with axonal decompensation, and worsening of function (Birnbaum and Stulc 2017).

Lastly, a double-blind, placebo-controlled trial (SPI2) with 642 patients who had no relapses in the two years before enrolment where 64% had secondary progressive MS and 35% had primary progressive MS was conducted. The primary endpoint was a composite of the proportion of participants with confirmed improvement in EDSS or TW25, and biotin was administered at 100mg TID. Thirty-nine (12%) of 326 patients in the biotin group compared with 29 (9%) of 316 in the placebo group improved at month 12. Twenty-nine (9%) participants in the biotin group and 31 (10%) in the placebo group experienced relapses, and no differences in MRI outcomes were observed (Cree et al 2020). The relapse and MRI outcomes may reduce concern raised by Tourbah and colleagues (2016, 2018) regarding higher disease activity with high-dose biotin.

It is unclear why the pilot trial of Sedel and colleagues (2015) results were greatly different from Cree and colleagues (2020) as both had similar age and initial EDSS. Mechanistically, it makes sense to include sufficient biotin nutritionally speaking as a factor for myelination but it appears that pharmacologic dosing of biotin does not consistently provide benefit. It is plausible that despite enhancing one rate-limiting enzyme involved in myelination that patients may lack other necessary cofactors for this process. One group estimated that a biotin intake of 1mg daily would come close to maximizing the activity of holocarboxylase synthetase in the central nervous system which is needed to catalyze the formation of biotin-dependent enzymes for myelin synthesis (McCarty and DiNicolantonio 2017). It is worth mentioning biotin ingestion frequently causes laboratory errors for numerous biotinylated immunoassay-based laboratory tests such as free thyroxine, free triiodothyronine, thyroglobulin, dehydroepiandrosterone sulfate (DHEA-S), estradiol, testosterone, ferritin, progesterone, vitamin B12, prostate-specific antigen, parathyroid hormone, luteinizing hormone, and follicle-stimulating hormone. With high dose biotin reported to have a half life of up to 18.8 hours discontinuation for a few days prior to lab work is suggested (Li et al 2020).

Vitamin A is a generic term for a number of related retinoid compounds such as retinol (an alcohol) and retinal (an aldehyde) also known as “preformed vitamin A”. Retinal can be converted by the body to retinoic acid (RA), the form of vitamin A known to affect gene transcription typically activating retinoic acid receptors α, β and γ (Bar-El Dadon and Reifen 2017, Huang et al 2018). Preformed Vitamin A is highly unstable. To enhance stability, esterification with palmitic and acetic acid have yielded retinyl palmitate and retinyl acetate, respectively (Souganidis et al 2013). RA exists in two significant derivatives: 9-*cis*-RA and all-*trans*-RA (Huang et al 2018). Oligodendrocyte lineage cells appear to express retinoic acid receptor RXR-γ in tissues undergoing remyelination. Administration of 9-*cis*-RA to demyelinated cell cultures and to aged rats after demyelination caused an increase in remyelinated axons suggesting that the RXR-γ is a positive regulator of OPC differentiation and remyelination (Huang et al 2011). The glycosphingolipids galactosylceramide (cerebroside) is the main sulfate acceptor in brain tissue to create sulfatide (the sulfated form) which are the

most common lipids in myelin. Dietary Vitamin A deficiency in the period of myelination heavily depressed the formation of sulfate and sulfatide in vitro compared to the activities of normal developing rats with an identical age (Clausen 1969). Clinically, 35 MS patients were divided into two groups where one group was given 25,000IU/day vitamin A (as retinyl palmitate); in the vitamin A group, the peripheral blood mononuclear cells showed reduced proliferation when stimulated with myelin oligodendrocyte glycoprotein (Jafarirad et al 2012). In another study, 101 RRMS patients where the treatment group was administered 25,000IU/day retinyl palmitate for six months followed by 10,000IU/day for another six months showed significant improvements for fatigue and depression possibly through anti-inflammatory mechanisms, and none of the patients were excluded from the study because of adverse effects (Bitarafan et al 2016). All-*trans*-RA and 9-*cis*-RA appear to modulate the imbalance of Th17 and Treg cells (Abdolahi et al 2015). Furthermore, treatment of T cells with RA attenuated their ability to induce disease in experimental autoimmune encephalomyelitis (EAE), a murine model for MS (Raverdeau et al 2016). Therefore, inclusion of vitamin A may not only help in part to facilitate myelination but may also have beneficial immunomodulatory effects. Similar dosing to these studies is suggested because of apparent benefit and safety demonstrated.

Vitamin K exists in two main natural forms: K_1 (or phylloquinone) and K_2 (menaquinone including several different vitamers). Menaquinones are classified according to the length of their unsaturated side chains from MK-4 (shortest) to MK-15. MK-4 is produced by systemic conversion of K_1, and MK-7 through MK-10 are synthesized by bacteria in humans (Fusaro et al 2017). Phylloquinone is mainly found in green vegetables. Liver is a rich source of menaquinones, which are also in meats, cheese and eggs (Cozzolino et al 2019).

MK-4 is the predominant form of vitamin K measured in the human brain and concentrations are higher in myelinated areas. As mentioned, pyridoxal 5'-phosphate is a cofactor for serine palmitoyltransferase and for sphingomyelin synthesis. These processes appear to depend on Vitamin K which influences the activity of galactosyl-ceramide sulfate transferase (also called cerebroside sulfotransferase), the enzyme that catalyzes the conversion of cerebrosides to sulfatides (Denisova and Booth 2005).

Vitamin K_2 levels were assessed in 45 MS patients (predominantly females with RRMS) and 29 healthy controls (also mostly women). The assay measured all varieties of K_2. The MS patients had more than three-fold lower K_2 blood levels than controls (235 ± 100ng/ml vs. 812 ± 154ng/ml, respectively) and female patients had significantly lower K_2 levels than males. Lower levels correlated with increased relapses per year. One proposed explanation was increased consumption of K_2 by tissues for remyelination (Lasemi et al 2018). Regarding MS, using the cuprizone demyelination model, mice were allowed to remyelinate in the absence or presence of K1, whose presence enhanced the production of total brain sulfatides (Popescu et al 2018).

Adequate intake for adult females is 90mcg and 120mcg daily for adult males and despite its fat solubility, no tolerable upper intake level has been set (Turck et al 2017). Pharmacologic doses

of 45mg/day of MK-4 to osteoporotic patients for 24 months has been shown to be safe (Shiraki et al 2000). Pharmacologic doses of 5mg of K1 for up to four years have also shown to be safe in post menopausal women (Cheung et al 2008). Vitamin K1 supplementation at 10mg/day for eight weeks was well tolerated in women with Rheumatoid Arthritis, perhaps further reflecting safety in autoimmunity (Shishavan et al 2016). Because MK-4 is the dominant form in the brain, contextually in MS it may be advantageous to ensure intake of MK-4 through animal sources and supplementation of at least 90-120mcg is recommended considering prevalence of deficiency if dietary intake is in doubt. Be advised that Vitamin K interacts with some medications such as anticoagulants possibly beyond intake of 150mcg daily (Violi et al 2016).

Iron also appears indispensable for myelin synthesis. Iron deficiency in early life is associated with hypomyelination. In both pre and post natal development, iron is an essential factor in myelination and oligodendrocyte biology, as disruption of iron availability in animal models results in a decrease in myelin proteins and lipids (Ortiz et al 2004). In the brain, cellular accumulation of iron is highest in oligodendrocytes which further implies a critical role of iron in their function (Hauser et al 2020). Many of the enzymes involved in the physiological pathways that produce myelin utilize iron as part of their catalytic center (such as lipid saturase and desaturase) and the demand for iron is also high because myelinogenesis is highly energy-intensive (Grishchuk et al 2015). Serum iron and ferritin concentrations were significantly lower in the MS subjects compared to matched controls with median ferritin 32.00 in MS patients versus 54.22 in controls in 27 females and 3 males (Van Rensburg et al 2006). Low ferritin may have implications for MS fatigue.

Data suggests that ferritin is the main iron transport mechanism to oligodendrocytes, as one molecule of transferrin or lactoferrin has the ability to carry two molecules of iron whereas, ferritin can bind up to 4,000 molecules of iron in its core (Hulet et al 1999). Ultimately, when one is attempting to encourage myelinogenesis, ensuring iron sufficiency is of importance, possibly by ensuring sufficient ferritin saturation. However, because age-related iron accumulation in the human brain is associated with neurodegeneration of progressive MS, it is reasonable to not do this in excess (Mahad et al 2015).

Manganese, copper and zinc appear to have roles in myelination but their exact roles are not well elucidated (Bourre et al 1987). In the Cuprizone MS model, cuprizone is a copper chelator, which when ingested by mice, causes copper deficiency and oligodendrocyte degeneration and demyelination (Popescu et al 2018). Clinically, until more is known, the inclusion of a general multivitamin with appreciable mineral content is warranted.

Citicoline is the generic name of cytidine-5′-diphosphocholine or CDP-choline, but this, as with other phosphorylated substrates, are considered unable to penetrate cell membranes (Grieb 2014). Citicoline is degraded to cytidine and choline during hydrolysis and dephosphorylation in the blood which easily pass the blood-brain barrier (Jasielski et al 2020). Endogenously, formation of citicoline from choline is the rate-limiting step in the synthesis of

phosphatidylcholine, as previously discussed as one of the most abundant lipids in myelin (Weiss 1995). In the CNS, acetylcholine synthesis is favored when the available amount of choline is limited, therefore choline is preferentially used to produce acetylcholine, which limits choline available for phosphatidylcholine production (Conant and Chauss 2004). Cytidine undergoes cytoplasmic conversion to cytidine triphosphate (CTP). Choline is phosphorylated by choline kinase into phosphorylcholine which combines with CTP to form citicoline. Citicoline then combines with diacylglycerol forming phosphatidylcholine (via choline phosphotransferase) for repair of neuronal membranes (the CDP-Choline Pathway or the Kennedy Pathway) (Clark et al 2008). Endogenously, choline is synthesised from ethanolamine by three successive methylations once again implicating MTHF and methylcobalamin (Van Rensburg et al 2006). Citicoline has other relevant neuroprotective effects which include reducing glutamate excitotoxicity, and supporting axon regeneration (Gandolfi et al 2020). Citicoline serves as an intermediate in the synthesis of sphingomyelin, another neuronal membrane phospholipid component (Adibhatla and Hatcher 2002).

Citicoline was studied in EAE (Experimental Autoimmune Encephalomyelitis) and in the cuprizone model of demyelination to test the hypothesis that Citicoline directly increases remyelination. In the EAE model, Citicoline ameliorated the disease course and exerted beneficial effects on myelin, oligodendrocytes and axons. After cuprizone-induced demyelination, it enhanced myelin regeneration and reversed motor deficits. An increase in the numbers of proliferating OPCs and oligodendrocytes were found. No differences were found in any immunologic parameters (T Cells, cytokines, microglia) between treatment and control groups, indicating the observed effects were not due to immunomodulation (Skripuletz et al 2015).

Relevant mechanisms of citicoline in MS include Sirtuin activation as treatment with citicoline increased SIRT1 protein levels in experimental models (Hurtado et al 2013). SIRT1 is a histone deacetylase that is involved in longevity and plays a role in neuronal health during aging (Herskovits and Guarente 2014). The choline moiety from citicoline can be metabolized to betaine, which serves as a source of methyl groups, and through metabolism to SAMe serves to turnover homocysteine to cysteine and ultimately glutathione which has neuroprotective qualities (Adibhatla and Hatcher 2002). Choline in citicoline is less prone to conversion to potentially atherogenic product trimethylamine N-oxide (TMAO); conversion to TMAO is mediated at the level of the gut whereas citicholine degradation happens in the blood (Synoradzki and Grieb 2019). Combined citicoline and DHA synergistically and significantly improved learning and memory ability in a brain ischemia model compared to either alone, indicating the concept of enhanced synergistic effects in neuronal injury (Nakazaki et al 2019).

Oral Citicoline dosed 500mg twice a day was effective and safe in the treatment of mild vascular cognitive impairment over a nine-month period (Cotroneo et al 2013). Doses of 2000mg daily have also been shown to be well tolerated in humans with antidepressant and cognitive enhancing effects over a 12-week period (Brown and Gabrielson 2012, Gavrilova et al 2011).

Therefore, 1000-2000mg daily for at least 12 weeks is a reasonable dose strategy to consider since both have been shown to have an effect on brain related parameters in humans.

Lithium has emerged as a neuroprotective agent through multiple mechanisms including inducing BDNF, inhibiting glycogen synthase kinase-3beta (GSK3β) activity and indirectly inhibiting N-methyl-D-aspartate (NMDA)-receptor glutamate-mediated calcium influx (Rowe and Chuang 2004). Inhibition of GSK3β stimulates OPC proliferation and myelination via the canonical Wnt signaling pathway by stimulating nuclear translocation of β-catenin (Azim and Butt 2011).

In one study, 44 RRMS patients were compared to 43 matched healthy subjects revealing a statistically significant difference with regards to serum lithium concentrations. Lithium was found to be remarkably lower in RRMS (0.57 ± 0.2μg/l) compared to controls (2.29 ± 0.7μg/l) (Karimi et al 2017).

In EAE, lithium carbonate administration has been studied in a dose strategy commonly used to achieve serum levels equivalent to those attained therapeutically in human patients. Pre-treatment with lithium markedly suppressed the clinical symptoms of EAE with reduced demyelination, microglial activation, and leukocyte infiltration in the spinal cord. Furthermore, lithium administered after disease onset reduced disease severity and facilitated partial recovery (De Sarno et al 2008). Converting the dose used in the trial, approximately 486mg would be used for a 60kg adult (Reagan-Shaw et al 2008).

Twenty-three patients with primary or secondary progressive MS were recruited into a two-year crossover trial in which subjects were randomly assigned to take a target of 300mg/day lithium carbonate, or 150mg/day if the larger dose was not tolerated in year one or two. Disability did not significantly change as measured by EDSS and MS Functional Composite. However, mood and mental parameters did improve. A possible stabilizing effect of lithium on brain volume was seen, but the study was underpowered to definitively detect change in brain volume as a therapeutic outcome (Rinker et al 2020).

Dosing for mood stabilization is frequently from 600 to 1200mg/day with necessary monitoring of renal and thyroid parameters (Malhi et al 2017). In a retrospective review of lithium usage in veterans with MS (to treat refractory mental health disorders), 101 veterans with MS who took lithium for more than six months were assessed. Annualized relapse rates were higher on Lithium but an increase in EDSS scores were greater in the off-lithium period than the on-lithium period. However, a consistent effect of lithium on MS disease activity was not apparent and its unclear if these subjects experienced a true acceleration of their disease or if their disease was independent of lithium treatment (Rinker et al 2013). Ultimately, it appears that therapeutic lithium dosing is not in and of itself highly beneficial with regards to improving disability.

Lithium orotate (LO) is non-prescription lithium source typically in doses of 5-20mg elemental lithium compared to 120-240mg elemental lithium in prescription lithium carbonate. LO dosing

is thought to mimic the levels of lithium gained from living in areas where there are relatively high concentrations of lithium in the food chain and water supply. Orotate is said to act as a delivery system to transport the lithium ion efficiently through the cell membrane to its various sites of action within the cell (Devadason 2018). Ultra low dose lithium (400mcg daily) can improve mood parameters indicating that despite the low dose, it may affect brain parameters. 100mcg daily of lithium has been suggested as the intake for American adults (Schrauzer and de Vroey 1994). Although doses used in Rinker and colleagues (2020) did not appear to significantly affect EDSS, and higher doses in Rinker and colleagues (2013) were not clearly effective, it may make sense to rectify the lower levels observed in Karimi and colleagues (2017) in the scenario that there is increased demand for lithium as part of the pathogenesis, and LO may fit the role of rectifying those deficiencies.

Non-Nutritional Approaches

Thymosin beta4 (Tβ4) is a 43-amino acid peptide isolated originally from a thymic extract (Goldstein et al 2005). Tβ4 is a potent regulator of actin assembly in living cells (Sanders et al 1992). Outside of the CNS, Tβ4 exerts anti-inflammatory and anti-fibrotic effects, has potential in hepatic disease and renal disease, promotes cell migration and angiogenesis and has potential in corneal and cardiac disease (Jiang et al 2017, Lv et al 2020, Sosne et al 2007, Vasilopoulou et al 2015).

In the CNS, Tβ4 can enhance angiogenesis, neurogenesis, neurite and axonal outgrowth, but is thought to principally effect oligodendrogenesis. Tβ4 is thought to target multiple molecular pathways that drive oligodendrogenesis possibly by altering cellular expression of microRNAs (Chopp and Zhang 2015). MicroRNAs are small noncoding RNAs that adjust gene expression in the transcription stage, and in particular, Tβ4 stimulates the expression of miR-146a which affects NF-κB (Nuclear factor kappa B, a proinflammatory signaling pathway) and may be anti-inflammatory controller in the CNS particularly regulating microglia (Shomali et al 2020).

Tβ4 is expressed in a wide variety of organs including throughout the CNS. Tβ4 is predominantly expressed in neurons as well as in microglia and neural progenitor cells with a number of repair functions related to cell proliferation, angiogenesis, and axonal remodeling (Pardon 2018). Tβ4 improves neurological functional outcome in a rat model of embolic stroke and traumatic brain injury (Morris et al 2012). Mice subjected to EAE were treated with saline or intraperitoneal Tβ4 and those with Tβ4 showed enhanced functional recovery and significantly increased OPCs and mature oligodendrocytes. Since the mature oligodendrocytes are post-mitotic and are unable to proliferate, it implies that the additional mature oligodendrocytes were from proliferating OPC differentiation (Zhang et al 2009). In a follow up study, EAE and the Cuprizone diet model were used to assess the effects of intraperitoneal Tβ4. Significantly increased OPC proliferation, mature oligodendrocytes, reduced axonal damage, enhanced remyelination and correlated functional recovery were seen in the Tβ4 treated EAE mice. Tβ4 treatment significantly increased OPC differentiation and remyelination in the Cuprizone model.

Tβ4 effects on generation and differentiation of OPCs is thought to be mediated through epidermal growth factor receptor (EGFR) signaling in this study (Zhang et al 2016). Tβ4 may mediate these effects without crossing the blood-brain barrier (Osei et al 2018).

Tβ4 has been studied in humans. Topically administered Tβ4 was shown to accelerate wound healing in patients with venous stasis ulcers (Guarnera et al 2010). Endothelial progenitor cells (EPC) pre-treated with Tβ4, and then transplanted in patients with acute ST segment elevation myocardial infarction had an increased six-min walking distance as well as enhanced cardiac function compared to non treated EPCs (Zhu et al 2016). Topically administered Tβ4 reduced dry eye sign and symptom assessments in those with severe dry eye disease (Sosne et al 2015).

With regards to parenteral human data, for potential use in cardiac ischemia, four cohorts, with ten healthy subjects each, were given ascending doses of either 42, 140, 420, or 1260mg intravenous Tβ4 or placebo for 14 days. Individuals at increased risk for malignancy were excluded from this trial because of the possibility of Tβ4 influencing the metastatic potential of certain malignancies through its ability to promote angiogenesis and stimulate cell migration. Adverse events were infrequent and mild or moderate in intensity, and there were no dose limiting toxicities or serious adverse events (Ruff et al 2010). Dosing 750mcg delivered subcutaneously daily for 30 days, then delivered every other day thereafter has been suggested although this has not been formally evaluated (Martinez 2019).

Quetiapine (Seroquel) is a second-generation antipsychotic that is used primarily for bipolar disorder and schizophrenia (El-Saifi et al 2016). With regards to myelination, (platelet-derived growth factor) PDGF-induced cell cycle activation seems to keep OPCs in a proliferative state and hinders OPC differentiation. Quetiapine inhibits PDGF-induced cell cycle activation and promotes oligodendrocyte differentiation (Mi et al 2018). Quetiapine has been shown to enhance the expression of several neurotrophic factors in vitro and in vivo, such as BDNF (Zhang et al 2012). In terms of neurodegeneration, Quetiapine treatment appears to increase the activities of antioxidant enzymes, including superoxide dismutase and glutathione peroxidase (Xu et al 2018).

Quetiapine was able to dramatically attenuate the severity of EAE symptoms by decreasing T cell infiltration into the spinal cord and suppressing local glial activation (microglia and astrocytes), and therefore diminishes the loss of mature oligodendrocytes and myelin breakdown. Furthermore, Quetiapine appeared to promote oligodendrocyte precursor differentiation because an increased number of mature oligodendrocytes were found after treatment (Mei et al 2012).

Insomnia affects approximately 50% of patients with MS (Alhazzani et al 2018). Quetiapine's antagonism of histamine H1 and serotonin type 2A receptors has a sedative effect and, as such, is widely used off-label as a treatment for insomnia. Quetiapine has been shown to improve sleep latency, total sleep time, and sleep efficiency compared with placebo at dosages of 25–75mg nightly and therefore can be considered a relevant agent for insomnia in MS patients (Anderson and Vande Griend 2014). Quetiapine has good tolerability at doses of 150 to 750mg/d for

antipsychotic effects. However, hangover, dizziness, dry mouth, increased hepatic transaminase levels and abdominal pain are reported side effects (Cutler et al 2002). The effective dosage range is usually 300-450 mg/day (Green 1999). It has efficacy in major depressive disorder possibly through dopaminergic action in doses between 150-300mg daily (Ignácio et al 2018). Depressive disorders occur in up to 50% of MS patients, with prevalence estimated to be up to three times higher than those of the general population and as such Quetiapine may be indicated because of the high prevalence of comorbid depression (Patten et al 2017). Monitoring metabolic parameters such as weight, blood pressure, glucose and lipids as well as thyroid function is recommended with long term (six months) administration, especially if dosed at greater than 100mg per day (Carr et al 2016). Overall, the effects of Quetipine on sleep, mood and possibly myelination and inflammation, in addition to it being readily available and low cost, make it an important agent to consider in MS. One group translated the dose commonly used in animals (10mg/kg) to roughly equal of oral treatment in humans (Zhornitsky et al 2013).

Iodine as iodide is taken up by the thyroid gland and through the iodization of tyrosine, T4 (thyroxine) and subsequently T3 (triiodothyronine) is produced (Zbigniew 2017). Iodine deficiency therefore appears to affect myelination indirectly through its intimate role in thyroid hormone production (Wei et al 2015, Zimmerman 2011). For instance, no myelination was detected in the cerebral cortex of fetuses aborted at month eight of gestation in an iodine-deficient area of China and gestational iodine deficiency in sheep and rodents reduces myelination (Prado and Dewey 2014). In the cuprizone mouse model, T3 thyroid hormone administration increased adult oligodendrocyte numbers and ameliorated aberrant astrogliosis (Zendedel et al 2016). During development, thyroid hormones also promote myelination by enhancing oligodendrocyte differentiation (Hartley et al 2019). The combination of T3 and quetiapine has been found to have an additive effect on OPC differentiation and consequent myelin production (Franco 2008). A phase 1 study looked at the maximum tolerated dose of T3 therapy over one week in 15 patients with MS in preparation for a phase II trial (Wooliscroft et al 2020). It is reasonable to consider optimizing Free T3 levels in an MS patient given that fatigue is one of the most common symptoms in MS and that it may impact myelination, possibly even more so in conjunction with quetiapine which can be thyrosuppressive (Manjaly et al 2019). Targeting T3 levels in the mid or upper normal range may denote an optimal replacement strategy which is frequently employed in naturopathic and functional medicine (Clarke and Kabadi 2004). Furthermore, iodine deficiency is one of the most common micronutrient deficiencies, yet is frequently overlooked, and iodine status can and should be assessed by determining urinary iodine concentration (Redman et al 2016).

Sleep disorders have a higher prevalence in MS patients and can be the consequence of an injury of specific CNS areas (Foschi et al 2019). It is somewhat commonsensical that sleep is involved in repair and the same applies to neurological repair and remyelination. Not surprisingly, sleep plays a role in some oligodendrocyte processes, including myelination (Buratti et al 2019). In fact, differential expression of genes occurs in oligodendrocytes during sleep; oligodendrocyte

genes involved in phospholipid synthesis and myelination or promoting OPC proliferation are transcribed preferentially during sleep. Therefore, it may be advantageous to dose discussed potential pro-myelinating substances before bed (Bellesi et al 2013). Adequate restorative sleep will likely serve to improve neurological repair, so screening for and rectifying sleep disorders is recommended.

Exercise, in terms of hormesis, could impose a mild stress on neurons resulting in activation of transcription factors that induce stress-resistant proteins like BDNF. Regular physical activity may have value in MS partly through other exercise-mediated neurotrophic factors like Insulin-Like Growth Factor (IGF-1) and Nerve Growth Factor (NGF) (White and Castellano 2008). Subcutaneously administered IGF-I upregulated synthesis of myelin proteins and myelin regeneration, and caused a dramatic improvement in EAE (Yao et al 1996). Intracerebroventricularly placed NGF prior to the induction of EAE has significantly reduced disease severity (Parvaneh Tafreshi 2006). Studies on motor rehabilitation support the notion that brain plasticity is preserved even in chronically disabled patients with MS, which suggests that exercise and rehabilitation are important elements to overcoming part of the physical disability (Prosperini et al 2015). In particular, task-oriented training best yields rehabilitation-induced plasticity (Prosperini and Di Filippo 2019). Electrically active axons are preferentially myelinated and this gives insight into the known positive influence of physical activity on wellbeing in multiple sclerosis (Lubetzki et al 2020). Exercise and rehabilitation may also induce compensatory adaptive changes irrespective of potential impact on myelination (Flachenecker 2015).

Hyperbaric Oxygen Therapy (HBOT) has several mechanisms relevant in mediating neurological injury including: increasing tissue oxygenation, reducing inflammation, decreasing apoptosis and promoting neurogenesis and angiogenesis (Hu et al 2016). There is evidence that repetitive HBOT improves outcomes in traumatic brain-injured patients, and animal models suggest that enhanced remyelination in the injured areas is part of the mechanism through which the HBOT works (Kraitsy et al 2014). Stem cell release is frequently reported with HBOT, for instance, neonatal hypoxic-ischemic rats treated with HBOT had proliferation of endogenous neural stem cells and an increase in newly generated neurons (Yang et al 2008). However, strong in vivo promyelinating effects have not been demonstrated in models of MS. Some promising human data has emerged. In a study, 40 patients with advanced chronic multiple sclerosis were randomly divided into two groups and treated at pressures of 2.0ATA (atmosphere absolute) for 90 minutes over twenty treatments with either pure oxygen or 10 percent oxygen. Objective improvement (mobility, fatigue, balance and bladder function) occurred in 12 of 17 patients treated with hyperbaric oxygen and in 1 of 20 patients treated with placebo (Fischer et al 1983). However, numerous other trials have failed to find a substantial effect evaluating HBOT over a course of twenty treatments (Confavreux et al 1986, Harpur et al 1986, Wiles et al 1986, Wood et al 1985). It has been suggested that 20 consecutive treatments may have been insufficient for the majority of those treated or that the treatment period was insufficient. For instance, one

longer term study looked at 44 MS patients (22 in the 100% oxygen group and 22 in the compressed normal air group) receiving 2.5ATA for 90 minutes initially for one month, then multiple "booster" treatments weekly over a one-year period. In the Hyperbaric group, 14/22 reported benefits, four reported no change and four declined. Whereas only two in the Hyperbaric air group reported benefit. Interestingly, it took six months before major changes were noted (Oriani et al 1990). At this point it appears that although not apparently detrimental, it is unclear whether only a subset of MS patients responds to HBOT or whether longer term treatment protocols are needed.

Synergistic Approaches

One group investigated the impact of a nutrient blend (containing DHA, arachidonic acid, vitamin B12, vitamin B9, iron and sphingomyelin) or each of these nutrients individually, on OPCs as well as their myelinating properties. In particular, the nutrient blend increased the number of OPCs and promoted their differentiation into oligodendrocytes. Each nutrient dose was selected based on a pilot study using, 1X, 10X or 100X of the known human adult cerebrospinal fluid concentration, using the highest dose with the least toxic effect. The beneficial effects seemed to be dose-dependent as lower doses of the blend failed, implying that human dosing might need to be supraphysiological or pharmacologic.

Treatments with iron, B12, folate and sphingomyelin all resulted in a positive effect on differentiation (albeit of a smaller magnitude) in vitro, suggesting that differentiation OPCs benefit, to some extent, from the net synergistic effect and interaction between nutrients compared to only using individual nutrients (Hauser et al 2020). It is note worthy that arachidonic acid, on its own, was inhibitory to every single myelination parameter perhaps suggesting excess omega-6 fatty acids may not be beneficial for myelination.

A study using a modified Paleolithic dietary intervention (MPDI), where eight subjects (one male) and nine controls (one male) completed the dietary intervention over a three-month period. The diet is described as nine cups of vegetables and some fruits, meat protein including organ meat, and complete abstinence from products containing gluten, dairy, potatoes, and legumes. Significant improvements were seen in Fatigue Severity Scale score, the Multiple Sclerosis Quality of Life-54 (mental and physical quality of life), and time to complete (dominant hand) 9-Hole Peg Test from baseline compared to controls. Subjects in both groups demonstrated improved gait but the MPDI group subjects tended to improve more than controls (Irish et al 2017).

The diet uses both plant and animal sources of Vitamin K. The diet maximizes many nutrients but the highest nutrient using this approach is Vitamin K. Increased vitamin K serum levels (262% increase from baseline) were observed in the subjects, and intake was estimated 600% of the adult adequate intake, with 533µg vitamin K per 1000kcals (Irish et al 2017). Since Irish and colleagues (2017) showed improved measurable parameters, with Vitamin K as the most

enhanced nutrient in the study, it may be sensible to maximize dietary Vitamin K sources in a clinical setting with patients in an attempt to mimic the positive effects shown.

MPDI style menu was assessed for nutritional adequacy and average % Recommended Dietary Allowance (RDA) was >300%. Vitamins B_1, B_2, B_3, B_6 and B_{12} were in excess of 500% RDA, likely due at least in part to the inclusion of nutritional yeast. On average, iron was 229.13%RDA, Zinc 224.88%RDA, Folate 262.88%RDA and Copper 378.50%RDA. Vitamin K levels were ≥888% Adequate Intake (AI) as the highest percentage of all nutrients, and Manganese was ≥ 269% AI and Choline was ≥91% AI, the lowest of the main identified myelinating nutrients (Chenard et al 2019). Therefore, although the results seen in Irish and colleagues (2017) seem to be weighted on Vitamin K, one cannot exclude the possibility that nutritional synergy contributed to the benefits seen.

In a 2020 trial, based on the premise of "reported neurologic synergistic effects of B1 (thiamine), B6 (pyridoxine), and B12 (cyanocobalamin)", sixteen patients diagnosed with RRMS and visual disability following acute optic neuritis, were given 300mg of vitamin B1 (as thiamine), 450mg of vitamin B6 (as pyridoxine) and 1,500mcg of vitamin B12 (as cyanocobalamin) for 90 days. As an addition to disease-modifying therapies this improved visual function parameters including visual acuity (Mallone et al 2020). It is worth nothing that the dose of B6 is supratherapeutic, and is likely unsafe for long term use as some cases of sensory neuropathies have been reported at doses of less than 500mg, but over 200mg per day intake for months (Hemminger and Willis 2020). The dose of thiamine is likely safe for long term use as 300mg daily orally is used in the treatment of diabetic neuropathy (Rabbani et al 2009). Furthermore, B1 doses up to 1500mg daily have been used parenterally in Wernicke encephalopathy (Latt and Dore 2014). As discussed above, B12 doses up to 60mg have been used (Kira et al 1994). Trials like these imply synergy between the B vitamins, however, if a low number of individual nutrients are used, they may require supratherapeutic dosing for effect.

In a six-month pilot study looking at a nutrient regimen designed to promote myelin regeneration, the "Raphah Regimen", which anecdotally showed symptom improvement of some MS subjects, was used. Iron supplements (15mg/day) were prescribed for those who presented with lower iron status. Essential amino acids, 500mg of Evening Primrose oil, 500mg of salmon oil, 300mg lecithin, and essentially a multivitamin and mineral were given. Of note, all B vitamins, zinc, copper and manganese were given. Methylation was optionally enhanced by additional weekly vitamin B12 injections, or a 1mg/day sublingual B12 supplement (presumably both methylcobalamin) or S-adenosyl methionine (SAMe) at 200mg/day (Van Rensburg et al 2006).

After six months, in 12 "compliant" RRMS patients, the mean total EDSS score improved significantly from 3.50 at baseline to 2.45 at endpoint with a large benefit in mood, whereas the EDSS in the "non-compliant" group had increased from 4.83 at baseline to 5.50. Both groups had significantly reduced homocysteine concentrations at six months, suggesting that

methylation is necessary but not solely sufficient for myelin regeneration (Van Rensburg et al 2006).

The authors commented on the synergistic use of a number of relevant nutrients as follows: “if myelin production is compared to a production line in a factory, it would be reasonable to provide all the raw materials in adequate quantities on a continuous basis rather than provide only one constituent at a high concentration.” In this study, myelination was implied through functional improvement. This in essence demonstrates that nutritional synergy can be essential for functional improvement and that pharmacologic dosing is perhaps not always essential as large doses were not utilized in this study (Van Rensburg et al 2006).

Preliminary Areas

Taurine is one of the most abundant amino acids in the brain and throughout the body. Taurine serves a wide variety of functions in the central nervous system including neuroprotection by suppressing glutamate-induced toxicity via inhibition of calcium influx (Ripps and Shen 2012). Levels of taurine were found to be elevated 20-fold during the course of oligodendrocyte differentiation and maturation. Furthermore, when taurine was added at physiologically relevant concentrations, it dramatically enhanced in vitro OPC differentiation and maturation (Beyer et al 2018). Taurine directly increases the intracellular availability of the amino acid serine, which serves as a critical building block for phosphatidylserine glycosphingolipid synthesis in myelination (Rosko et al 2019). Taurine at 1500mg daily in conjunction with exercise has been shown to decrease inflammation, maintain blood-brain barrier integrity and enhance cognition in older adults (Chupel et al 2018, Chupel et al 2021).

Creatine is a nonessential amino acid that does not enter into protein composition (Balestrino and Adriano 2019). Creatine, through its intermediate phosphocreatine, provides a necessary cellular reserve of high-energy phosphates for ATP formation (Ryu et al 2005). Data that suggest creatine synthesis is required for the survival of newly generated oligodendrocytes during remyelination and that the administration of creatine into the CNS significantly improves oligodendrocyte viability during CNS remyelination, likely through enhanced energetics (Chamberlain et al 2017).

Pyrroloquinoline quinone (PQQ) is water soluble quinone distributed ubiquitously in nature and found in numerous dietary sources, including tea, green peppers, parsley, kiwi fruit, but is not endogenously produced by humans. PQQ is well known to have the ability to catalyze continuous redox cycling (Akagawa et al 2016). Nerve growth factor (NGF) was the first neurotrophin discovered for its stimulatory effect on differentiation, survival, and growth of neurons in peripheral and central nervous system (Colafrancesco and Villoslada 2011). NGF has been found to promote synthesis of myelin sheaths by myelin forming cells in CNS and PNS, as well as differentiation of oligodendrocytes (Razavi et al 2015). NGF promotes axonal regeneration, facilitates migration of OPCs to the sites of myelin damage and NGF induces the production of BDNF (Acosta et al 2013). PQQ stimulates NGF and was found to be a potent

enhancer for the regeneration of peripheral nerves in a sciatic nerve model (Liu et al 2005). In a Parkinson's model, PQQ suppressed the up-regulation of pro-inflammatory factors, such as IL-1β, IL-6 and TNF-α from microglia (Zhang et al 2020). Effects on human brains have been demonstrated as PQQ improved cognitive function in humans by improving regional cerebral blood flow and oxygen metabolism at a dose of 20mg (Nakano et al 2016).

Lion's Mane (*Hericium erinaceus*) diterpenoids erinacine A, B, and C, from its mycelia, is another well known natural health product that stimulates NGF synthesis (Friedman 2015). Lion's Mane promoted the regeneration of peripheral nerves in an animal model (Wong et al 2012), and it also triggered neurite outgrowth in brain and spinal cord cells in vitro (Samberkar et al 2015), though the immunostimulatory potential of its polysaccharides in the context of MS have not been elucidated. However, oral intake was shown to ameliorate experimental colitis by suppressing TNF-α, IL-1β, and IL-6 in colon tissues as well as adjusted the production of nitric oxide, malondialdehyde, and superoxide dismutase in serum to suppress oxidative stress, which suggests it might in fact be immunomodulatory (Qin et al 2016). Lion's Mane may also reduce microglial activation (Kushairi et al 2019).

Short-chain fatty acids (SCFAs) are produced in the colon by bacterial fermentation of non-digestible carbohydrates like soluble dietary fiber and have been shown to have immunomodulatory effects (Prasad and Bondy 2018). SCFAs can cross the blood-brain barrier (Wenzel et al 2020). Lack of SCFAs exist in MS patients, as gut dysbiosis and a depletion of fecal acetate, propionate, and butyrate was observed in MS patients compared to healthy controls (Zeng et al 2019). Short-chain fatty acids have been shown to ameliorate the disease course in EAE (Melbye et al 2019). Oral administration of antibiotics significantly enhanced cuprizone-induced demyelination whereas oral administration of butyrate significantly ameliorated demyelination independent of microglia. Furthermore, butyrate treatment facilitated the differentiation of immature oligodendrocytes, exemplifying the role of a healthy microbiome even in the context of demyelination (Chen et al 2019).

The mechanisms that regulate OPC differentiation are dysregulated in the aging brain, and preliminary evidence exists for caloric restriction as a restorative strategy. Fasting or treatment with metformin was found to restore the regenerative capacity of aged OPCs, improving remyelination in aged animals following focal demyelination (Neumann et al 2019). In mice, three, three-day cycles of a very low calorie and low protein fasting mimicking diet (FMD) (where on day one they consumed about 50% of their normal caloric intake and on days two to three they consumed about 10% of their normal caloric intake), showed reduced clinical severity in all mice and completely reversed symptoms in 20% of animals, as well as promoted OPC regeneration and remyelination in both EAE and cuprizone MS models. Mechanistically, up-regulation of AMP-activated protein kinase (AMPK) or down-regulation of mTOR Complex 1 (mTORC1), which contains the kinase mTOR, were proposed. AMPK and mTOR both sense nutrient availability and dictate cell fate (Choi et al 2016). Both mTOR and AMPK are considered master regulators of cell survival and metabolism (Garza-Lombó et al 2018).

Furthermore, a modified FMD where 1/3 of control calories are consumed for three days, followed by ad libitum feeding for two cycles had significant decreases in EAE severity, immune cell infiltration in spinal cord, CNS demyelination, enhanced BDNF and improved remyelination markers such as expression of myelin basic protein and proteolipid protein (Bai et al 2021).

Summary of Clinical Recommendations

Omega 3 fatty acids – minimum of 1.98g EPA and 1.32g DHA per day (possibly with a low-fat diet)
Daily high potency B complex, possibly with MTHF, methyl and adenosylcobalamin
Biotin – 1mg per day
Daily multivitamin with zinc, copper, manganese
Vitamin K2 – 90-120mcg MK-4 or higher per day
Vitamin A – 25 000IU per day initially, then 10 000IU per day maintenance after six months
Citicoline – 1000-2000mg per day
Lithium Orotate – 5-20mg per day
Addition of quetiapine and/or liothyronine/triiodothyronine, and/or thymosin beta4
Restorative sleep and daily exercise and/or physiotherapy
Consideration of: taurine, creatine, PQQ, lion’s mane and intermittent fasting

Concluding Thoughts

Finding remyelinating therapies to restore neuronal function and prevent axonal degeneration is still in its infancy yet is desperately needed. Although pharmaceutical strategies are in development, the use of principally nutritional techniques to hasten myelination is a promising area considering the pervasive roles and preliminary effects of nutrients identified herein. Because some patients are able to spontaneously remyelinate, identification of barriers to myelination for others is of utmost clinical interest. The possibility arises that some patients deficient in one or more nutrients may therefore impede the spontaneous remyelination process that can occur. Evidence exists for synergistic nutritional treatment as a promising area, in part because pharmacologic dosing of a single nutrient such as biotin has yielded suboptimal results. Finally, the use of existing agents known to enhance the well-known issue of OPC differentiation alongside synergistic nutritional strategies is worthwhile to explore for those currently suffering until better strategies are produced.

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Palmitoylethanolamide (PEA): Clinical Applications

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None

Conflict of Interest

The Author declares no conflicts of interest.

Palmitoylethanolamide (PEA): Clinical Applications

Abstract

Natural narcotics - opiates and cannabis - are within the prescribing authority of naturopathic physicians in some jurisdictions.

Cannabidiol (CBD) has been serviceable for neuropathic pain, but with limitations, not the least of which is financial toxicity. A new cannabinoid-like natural remedy for pain, central and peripheral neuropathy is the phospholipid palmitoylethanolamide (PEA). PEA occurs naturally in peanuts, soybeans, egg yolks, and the human body. PEA is an endogenous fatty acid amide, a phospholipid which is analgesic via G-protein-coupled receptors. PEA is a nuclear factor agonist, neuroprotective, and neuroregenerative, reducing neuronal inflammation and edema. It has been found effective for sciatica, migraine, endometriosis, dysmenorrhea, chemical neuropathy, TMJ, and more, in human RCTs and meta-analyses. Adverse effects are unusual, with occasional mild gastrointestinal upset reported. The aim of this review is to discuss a novel approach on neuropathic pain management, which is based on the knowledge of processes that underlie the development of peripheral neuropathic pain; in particular focused on the role of glia and mast cells in pain and neuroinflammation.

The Pain Problem

Pain is what you feel. Unpleasant and uncomfortable, pain is a very subjective experience of noxious stimuli. A trauma, injury or noxious exposure sets off an alarm in local nerve endings. Signals include bradykinins, substance P, histamine and prostaglandins. Nerve endings pick up the signal and transfer it to spinal pathways. Afferent pain impulses enter the spinal dorsal horn ganglia and synapse with interneurons in the substantia gelatinosa. Signals then ascend the lateral spinothalamic tract to the reticular formation in the brain stem pons and medulla. It is switched through the thalamus to higher brain areas. Pain is constructed by the brain. Functional MRI studies demonstrate that pain is only partially created by a sensory stimulus. The prefrontal areas of the brain evaluate the potential for harm, and the expectation of relief.

Gate control theory explains how counter-irritation such as massage or hot pepper extracts can block pain signals. Peripheral nerve stimulation can create excessive traffic which “blows the fuse” so the cord “shuts the gate” to the central nervous system. Needling or laser acupuncture may also work in part by counter-irritation/gate control, but also increase CNS production of analgesic chemicals that modify or inhibit pain, called endorphins and enkephalins (Cheng 2014).

Naturopathic physicians have many modalities to ease suffering, but pharmaceuticals are often the default remedies for acute or severe pain situations. Natural analgesics such as wintergreen,

Jamaican dogwood and white willow bark have limited utility. In British Columbia we are only permitted to prescribe one opiate, the synthetic drug Tramadol. Most wisely refrain from using it.

Mechanical damage such as traumatic brain injury, or nerve impingement, may each require completely different therapeutics. Compressed nerves and sciatica may be treated with manipulation, injection and physiotherapy. TBI and stroke require healing of reperfusion injury with vascular restoratives such as grapeseed extract, plus nutritional support-omega 3 oils, magnesium, and active B-complex.

Neuropathy from chemotherapy can be reduced with concurrent remedies such as thiamine, and L-glutamine. Natural medicines for neuropathy include alpha lipoic acid, acetyl-L-carnitine, methylcobalamin, n-acetyl-cysteine, agmantine sulphate, pyridoxal-5-phosphate, pyrroloquinolone quinone (PQQ), acupuncture, homeopathy, and hydrotherapy (McKinney 2020).

Cannabinoids are natural plant analogues of our innate endocannabinoid system, which regulates most biological functions and maintains homeostasis. Receptors for endocannabinoids anandamide (AEA) 2-arachidonolylglycerol (2-AG) are actually more abundant in humans than are opiate receptors. CB1 receptors for endocannabinoids are particularly abundant in the central nervous system, also in adipose tissue, liver, lungs, uterus, and placenta. Activation of CB1s in central and peripheral nerves can be analgesic. CB1 receptors on spinal GABA interneurons which can disinhibit pain projection neurons. Neurotransmitters modulated by cannabinoids include acetylcholine, norepinephrine, dopamine, 5-hydroxy-tryptamine, GABA and D-aspartate. Modulators of the endocannabinoid receptors impacts somatic, visceral, and neuropathic pain, and show clinical value for hyperalgesia, allodynia, pain of inflammation, and muscle spasticity (Piomelli 2003).

Cannabidiol (CBD) from hemp or marijuana has been serviceable for neuropathic pain, but with limitations, not the least of which is financial toxicity. CBD interacts strongly with CB1 receptors and may also decrease inflammation via the A2A adenosine receptor, which also down-regulates dopamine and glutamate in CNS (Argueta et al 2020).

CBD also interacts with the vanillinoid receptor system aka TRPV1 receptor, which is also activated by eugenol from cloves, and capsaicin from chili peppers (Kleckner et al 2019, Sledzinski et al 2018).

The narcotic and psychotropic cannabinoid from cannabis is tetrahydrocannabinol (THC). Severe pain requires both THC and CBD (Abrams et al 2011, Martin-Sanchez et al 2009). While 20mg THC has the analgesic effects of about 120mg of codeine, THC gives significantly more psychiatric effects. Large doses also incur considerable financial toxicity.

Other plants with cannabinoid-like activity:

- *Theobroma cacao* (chocolate) – anandamine.
- *Piper nigrum* (black pepper) – guineensis.

- *Echinacea purpurea* (coneflower) – N-alkyl amides.
- *Helichrysum italicum* (curry aster) – cannabigerol.
- *Piper methysticum* (kava) – yangonin kavalactone.
- *Tuber melanosporum* (black truffle) – anandamine.
- *Rhododendron anthopogonoides* – CBC, CBL, CBT.
- *Acmella oleracea* (electric daisy) – N-isobutylamides

Pain Relief from Food Sources – PEA - Palmitoylethanolamide

Palmitoylethanolamide (PEA) is a nutraceutical endocannabinoid that was retrospectively discovered in egg yolks. Feeding poor children with known streptococcal infections prevented rheumatic fever. Subsequently, it was found to alter the course of influenza (Ganley et al 1958). This natural phospholipid was later also found in peanuts, soybeans, and the human body (Paladini et al 2016, Petrosino and Di Marzo 2017).

PEA (C16:0 *N*-acylethanolamine), a lipid mediator biologically synthesized in many plants as well as in cells and mammal tissues belongs to the class of non-endocannabinoid (NAE) compounds that are much more abundant than the endocannabinoid anandamide in several animal tissues and endowed with important biological actions (Beggatio et al 2019).

PEA targets nonclassical cannabinoid receptors rather than CB1 and CB2 receptors. PEA indirectly activates classical cannabinoid receptors by an entourage effect with vanillinoid receptors (Mattace et al 2014). PEA may indirectly activate CB1 and CB2 receptors by acting as a false substrate for fatty acid amide hydrolase (FAAH), the enzyme involved in the degradation of the endocannabinoid AEA (Petrosino et al 2019, Petrosino et al 2017). This action leads to increased levels of AEA and, in turn, an increased activation of cannabinoid receptor-mediated signaling.

There are no reported drug-drug interactions and very few reported adverse effects from PEA, having demonstrated high safety and tolerability (Davis et al 2019, Gabrielsson et al 2016, Nestmann 2016, Petrosino and Di Marzo 2017). PEA is virtually non-toxic at doses of 600 mg twice daily as commonly used in case reports and studies (Germini et al 2017). Relevant PEA-induced side effects were not seen in humans at oral doses of up to 1,800mg/day. PEA has proven efficacious in humans in a number of clinical settings, including a significant number of prospective and randomized trials demonstrating the pain-relieving effects of PEA. There is lesser evidence of benefit in patients with non-pain symptoms related to depression, Parkinson disease, strokes, and autism. None of the clinical trials with PEA to date have reported significant adverse effects, only occasional mild gastrointestinal upset (Beggatio et al 2019, Nestmann 2016).

Food source ALIAmides (autacoid local injury antagonist amides) like PEA can also counteract the inflammatory cascade, in both acute and chronic inflammatory pathologies (Peritor et al 2019, Tsuboi et al 2018).

N-acylethanolamines such as palmitoylethanolamide exert anti-inflammatory, analgesic, and anorexic effects through nuclear receptors for peroxisome proliferator-activated receptor α (Tsuboi 2018). PEA is an endogenous PPAR-α ligand which modulates mitochondrial oxidative capacity and oxidative stress, influencing fatty acid and glucose metabolic flexibility (Annunziata et al 2020). PEA increases the levels of CB2 receptor mRNA and protein as a result of PPAR-α activation, and this effect is involved in PEA-induced microglia changes associated with increased migration and phagocytic activity (Guida et al 2017). PEA is an abundant acylethanolamide produced in the central nervous system (CNS) by neurons and glial cells. Anti-hyperalgesic and neuroprotective properties of PEA have been mainly related to the reduction of neuronal firing and to control of inflammation. PEA modulation of PPAR-α has been implicated in its beneficial impacts on peripheral neuropathies such as diabetic neuropathy, drug-induced peripheral neuropathy, carpal tunnel syndrome, sciatic pain, osteoarthritis, low-back pain, failed back surgery syndrome, dental pains, neuropathic pain in stroke and multiple sclerosis, chronic pelvic pain, postherpetic neuralgia, and vaginal pains. (Hesselink and Hekker 2012). PEA appears to benefit neuropathic pain from chemotherapy drugs, and restores myelinated fibre function lost to these neurotoxins (Hesselink 2013, Truini et al 2011). Acute neuropathy from diabetes or trauma also improved with PEA (Cocito et al 2014, Gatti et al 2012).

ALIAmides represent a group of endogenous bioactive lipids, including PEA, which play a central role in numerous biological processes, including pain, inflammation, and lipid metabolism. These compounds are emerging thanks to their anti-inflammatory and anti-hyperalgesic effects, due to the down regulation of activation of mast cells. Collectively, preclinical and clinical studies support the idea that ALIAmides merit further consideration as a therapeutic approach for controlling inflammatory responses, pain, and related peripheral neuropathic pain. (D'Amico et al 2020).

PEA is an endogenous endocannabinoid acting both centrally and peripherally, via G-protein-coupled receptors GPR 55 and GPR 119, influencing potassium and other membrane channels. GPR55 forms receptor heteromer with either CB1 or CB2 receptors (Balenga et al 2014, Martínez-Pinilla et al 2014, Martínez-Pinilla et al 2019). The anti-neuroinflammatory effects of PEA might be mediated, at least in part, by GPR55 activation (Kallendrusch et al 2013).

PEA is a nuclear factor agonist, reducing neuronal inflammation in part by mast cell modulation (De Fillipis et al 2013). PEA controls mast cell degranulation and substance P (SP)-induced histamine release in rat basophilic leukemia (RBL-2H3) cells, a mast cell model. PEA stimulation of 2-AG biosynthesis leads to activation of CB2 and thus to the inhibitory effects on degranulation (Petrosino et al 2019). The down regulation of mast cell activation in glial cells explains a great deal of the ability of PEA to abolish neuroinflammation (Paladini et al 2016). PEA reduces neuronal edema, is neuroprotective, restorative, and potent for pain (Artukoglu et al 2107). PEA has been studied and found helpful for lumbosacral sciatica (Domínguez et al 2012), failed back surgery syndrome (Paladini et al 2017), carpal tunnel syndrome (Faig-Marti and Martínez-Catassús 2017), and inflammatory bowel syndromes (IBS) (Couch et al 2017, Cremon

et al 2017). A randomized clinical trial compared the effect of PEA with ibuprofen, a nonsteroidal anti-inflammatory drug (NSAID) for pain relief in temporomandibular joint disorder (TMJ), osteoarthritis and arthralgia. PEA demonstrated effective antagonism to autacoid local inflammation, and modulated mast cell behavior, controlling both acute and chronic inflammation (Marini et al 2012). In a rat model of osteoarthritis PEA was compared to the NSAID drug meloxicam. PEA co-ultramicronized with the natural antioxidant quercetin (PEA-Q) showed superior effects compared to meloxicam, with none of the long-term adverse effects seen with NSAIDS (Britti et al 2017).

Sublingual ultra-micronized PEA was found to significantly reduce migraine headache days per month, duration and intensity of pain crisis, and number of analgesics taken per month. Thermographic testing of migraine sufferers showed a reduction of hypothermia as well as the response to trigger factors. No serious adverse events were observed (Volta et al 2016).

PEA appears to be highly effective for pelvic pain in young women, for example from dysmenorrhea (Tartaglia et al 2015). Endometriosis pain can be completely debilitating, with the pain being driven by inflammation linked to degranulating mast cells. Women with endometriosis treated for three months with oral PEA 400mg and polydatin 40mg, twice daily for 90 days showed reduced deep dyspareunia, dyschezia, dysuria, dysmenorrhoea, and analgesic drug use in all subjects. Additionally, some improvements in endometriotic lesions were demonstrated by imaging (Indraccolo and Barbieri 2010). The efficacy of the palmitoylethanolamide-polydatin combination for controlling chronic pelvic pain was later confirmed in a meta-analysis (Indraccolo et al 2017). Micronized palmitoylethanolamide-polydatin also reduced pain and urinary frequency in interstitial cystitis and other bladder pain syndromes (Cervigni et al 2019).

Growing evidence suggests that PEA may be neuroprotective during CNS neurodegenerative diseases, such as Parkinson's and Alzheimer's diseases, by switching off inflammation caused by mast cell activation (Skaper et al 2015). Mechanisms of action include modulation of peroxisome proliferator-activated receptor (PPAR) (Ye et al 2020) which controls calcium ion (Ca^{+2})-activated intermediate-and/or big-conductance potassium ion (K^{+}) channel opening, a driver of neuronal hyperpolarization. This is reinforced by the increase of the inward chloride ion (Cl^{-}) currents due to the modulation of the GABA receptors and by the desensitization of the TRPV1 receptors. PEA blunted Aβ-induced neuroinflammation in an in vitro rodent model of Alzheimer's (Scuderi et al 2011) by significantly diminishing either the altered expression of pro-inflammatory molecules, such as cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), or the enhanced release of prostaglandin PGE2, nitric oxide, IL-1β, and TNF-α. A PPAR-α antagonist was able to partly blunt the PEA-induced effects against Aβ-induced astrogliosis and neuroinflammation, thus suggesting a significant, but not exclusive, involvement of the PPAR-α in mediating these PEA effects (Paterniti et al 2013). PEA critically diminished the activation of p38 and Jun N-terminal kinase (JNK), as well as the subsequent activation of nuclear transcription factors, such as nuclear factor kappaB (NF-kB) and activator protein 1 (AP-

1) (Beggatio et al 2019). This gene transcription-mediated mechanism sustains the long-term anti-inflammatory effects, by reducing pro-inflammatory enzyme expression and increasing neuro-steroid synthesis. Overall, the integration of these different modes of action allows PEA to exert robust control over neuron excitability and neuronal inflammation, maintaining cellular homeostasis (Raso 2014).

PEA used for one year at 600mg daily slowed down Parkinson's disease progression and disability (Brotini et al 2017).

Some lesser evidence suggests other uses for PEA besides pain syndromes. PEA apparently reduces atherosclerotic plaque by promoting an anti-inflammatory and pro-resolving phenotype of lesional macrophages (Rinne et al 2018). PEA moderated eczema, and allergic dermatitis in a canine model (Cerrato et al 2012). Inflammation as well as glutamate excitotoxicity have been proposed to participate in the propagation of autism. PEA prevents glutamatergic toxicity and may augment therapeutic effects of risperidone on autism-related irritability and hyperactivity in children (Khalaj et al 2018)

In major depressive disorder there was a rapid onset of improvement with PEA given as an adjunct to Citalopram standard of care, with no additional adverse effects (Ghazizadeh et al 2018).

Summary

PEA is a natural food-source pain reliever with an unusual safety to efficacy profile. It is useful in a wide range of acute and chronic neurological injuries and diseases, and combines well with other therapies. Research suggests doses of 600 to 800mg twice daily for pain and acute conditions, yet as little as 600 to 800mg once daily for chronic conditions.

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A Low FODMAP (Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols) Diet Update

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A Low FODMAP (Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols) Diet Update

Abstract

Since their introduction into the nutrition world in the mid 2000s, fermentable carbohydrates, commonly knowns as FODMAPs have gained significant interest for their application as a low FODMAP diet to help those suffering with bowel disorders. Irritable bowel syndrome has a significant and growing prevalence around the globe, with limited successful interventions. However, following a low FODMAP has shown remarkable benefit. Low FODMAP foods contain low levels of fermentable and prebiotic fibers, which raise concerns of overall gut health, in those eating a low FODMAP diet since it is established that these fibers contribute to a healthy microbiome. This is one of a number of concerns surrounding the use of the low FODMAP diet for those suffering from bowel disorders, discussed below.

Introduction

Following a diet low in fermentable carbohydrates, now commonly known as the low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) diet, has gained popularity since its introduction to the nutrition world in the mid 2000s (Gibson and Shepherd 2005). Over the past 16 years the mechanisms of action, food content of FODMAPs, efficacy of the diet, as well as doubts and concerns have been extensively studied. Much of the research has been focused around solidifying the hypothesis that following a low FODMAP diet (LFD) benefits those with irritable bowel syndrome (IBS). The use of the LFD in other bowel disorders including inflammatory bowel disease (IBD) is increasing. While results have been promising, as with many medical advances there can always be drawbacks, the LFD not being an exception.

As review, FODMAPs can be found in a range of very common foods such as fruits, vegetables, legumes and cereals, honey, milk and dairy products, and sweeteners. All FODMAP are potential triggers, but fortunately, not all FODMAPs aggravate the same symptoms in patients with irritable bowel syndrome (Bellini et al 2020). Food processing techniques, plant cultivars, and growing conditions can all impact the FODMAP level in foods (Varney et al 2017). Monash University researchers were the first to come up with extensive lists of the content of FODMAPs in foods. Researchers around the globe have continued to study the content of FODMAPs in foods which is important to facilitate nutrition intervention and therapies (Liljebo et al 2020) and to be able to apply the diet internationally (Varney et al 2017).

Low FODMAP in Irritable Bowel Syndrome

The prevalence of IBS is estimated to be 11% globally, and much higher in certain countries including Canada and the United States (Canavan et al 2014). While not life threatening, it is well established that the effects of IBS significantly impact the quality of life of those that suffer from it. The LFD has been a beacon of hope for people with IBS, especially since many identify food as trigger for symptoms, but dietary interventions were not always a first line treatment.

Up to 80% of people with IBS feel benefit when following a LFD (Hustoft et al 2017). Three meta-analyses have shown that a diet low in FODMAPs effectively reduced functional gastrointestinal symptoms in those with IBS and is safe for short term use (Marsh et al 2016, Schumann et al 2018, Varjú et al 2017). Dionne and colleagues (2018) also found that a LFD is effective in reducing global symptoms in IBS patients, but they reported the evidence is 'very low quality'. In a recent study, the LFD was shown to specifically improve IBS symptoms such as abdominal pain, bloating, stool consistency, perceived severity of disease, and physical and mental components of quality of life; particularly in patients who suffer from diarrhea predominant IBS (IBS-D) patients (Cingolani et al 2020). The same researchers suggested the LFD seems to show greater feasibility for patients with more time to dedicate to the diet, more motivation, and more severe clinical features. This is a common concern with regard to the LFD, that it is time consuming and difficult to follow (Weynants et al 2020).

Due to the increase in popularity of the low FODMAP diet for the management of IBS, it is often self-prescribed and self-led. Sometimes it is suggested by general practitioners or gastroenterologists, however, evidence supports the use of dietitian-led education, in both individual and group delivery models (O'Keeffe and Lomer 2017). The 2019 Canadian Association of Gastroenterology Clinical Practice Guideline for the Management of IBS document states that "If a low-FODMAP diet is suggested, it should be implemented under the guidance of a dietician, and a strict diet should be implemented for as short a term as possible (e.g., four weeks)" (Moayyedi et al 2019). In a qualitative study by Trott and colleagues (2019), patients with IBS that were provided LFD information from their GPs and gastroenterologists reported that the information provided was difficult to apply in "real life". One major concern without proper education and guidance is the length of time that people will continue with the LFD and the downstream consequences that may occur. In a review by Whelan and colleagues (2018) three phases of a LFD are outlined; FODMAP restriction; FODMAP reintroduction; and FODMAP personalisation (Whelan et al 2018). They suggest that it is important for doctors, dietitians and patients to appreciate that this is not a 'diet for life' but, instead, an approach to dramatically reduce FODMAP intake below the level at which they induce functional gut symptoms. Dionne and colleagues (2018) report that LFD exclusion for two to six weeks should be viewed as a diagnostic test to identify IBS patients who are sensitive to FODMAPs. Those who fail to improve should not continue the diet. Those who improve should be instructed on reintroducing foods which contain FODMAPs to determine their personal sensitivities and tolerance thresholds. This information should then be used to liberalize and personalize the low

FODMAP diet with the intention of improving adherence and minimizing effects on the gut microbiome. In a randomized double blind, placebo-controlled study by Hustoft and colleagues (2017), a LFD improved symptoms in patients with IBS after only three weeks.

Among the concerns of adhering to a LFD long term are the potential changes in colonic microbiota composition. The LFD is by nature a diet low in prebiotic fibers and has been shown to reduce intake of prebiotic fructans and galacto-oligosachrrides (GOS) from the diet by up to 50 % (Böhn et al 2015, Staudacher et al 2012). These non-digestible carbohydrates typically increase the levels of bifidobacteriaceae and lactobacillaceae families in the gut of healthy individuals. Not surprisingly, following a LFD can cause a reduction in bifidobacteria and an increase in bacteria associated with dysbiosis (Vandeputte and Joossens 2020). After only four weeks of following the LFD, Staudacher and colleagues (2012) saw a significant reduction in luminal bifidobacteria concentration. Halmos and colleagues (2015) found a reduced total bacterial abundance in the feces by an average of 47% (when compared to a typical Australian diet). Vandeputte and colleagues (2020) suggest that supplementation with probiotics could be considered to partly counteract these changes. In a 2017 randomized controlled trial, researchers gave patients eating a LFD two sachets of multi-strain probiotic daily (450 billion bacteria per sachet) or placebo sachets, and found that those in the treatment group had greater abundance of Bifidobacterium species, and reported ‘adequate symptom relief’ more than patients receiving the placebo (Staudacher et al 2017). Some studies have shown that short-chain fatty acids (SCFAs) may also be negatively affected after following a LFD (Hustoft et al 2017), however, other studies have found no effect (Halmos et al 2015).

Nutritional Adequacy

An often-cited concern of the LFD is nutritional inadequacy, most notably, total energy, carbohydrate, fiber, calcium and iron (Hill et al 2017 , O’Keeffe et al 2018, Staudacher et al 2012). In 2020, Staudacher and colleagues conducted a secondary study of two randomized controlled trials where they looked at the habitual nutrient intake, diet quality, and diversity in participants with IBS and the effect of a four-week LFD on these parameters compared with controls. They concluded that in IBS, many individuals failed to meet national recommendations for a number of nutrients, including fat, fiber, iodine, and selenium. A LFD, when delivered by a dietitian, did not significantly impact the intake of most nutrients or diet diversity, however, it led to lower diet quality compared with controls (Staudacher et al 2020). Diet quality was a measure of how closely the diet aligns with dietary guidelines, based on World Health Organization dietary guidelines for the prevention of chronic disease.

Another concern of adhering to a LFD is a possible reduction in fiber intake if whole grain wheat products and high FODMAP fruits and vegetables are not replaced with suitable alternatives. A decrease in dietary fiber can lead to, or exacerbate, constipation especially in those with IBS. Research results are very mixed, with some studies showing that the LFD does indeed lead to a decrease in fiber intake (Böhn et al 2015), while others showed no difference (Eswaran et al

2016). Harvie and colleagues (2017) found that during the LFD, fiber intake decreased below 30 grams per day for males, and 25 grams per day for females, which is below the recommended numbers for many countries, including Canada. However, they did note that once study participants re-introduced FODMAPs to a tolerable level, fiber content of the diet returned to pre-intervention levels.

Low FODMAP Diet in Inflammatory Bowel Disease

While the majority of research surrounding the LFD is in regard to IBS, there have been an increasing number of studies looking at its effects in patients with IBD. In 2009, a pilot study by Gearry and colleagues showed that the low FODMAP diet may be the first effective dietary therapy for patients with IBD with coexistent functional gut symptoms. Interestingly, a randomized, placebo-controlled, cross-over re-challenge trial by Cox and colleagues (2017) found that of the FODMAPs examined it was fructans, but not GOS and sorbitol that induced gastrointestinal symptoms in patients with quiescent IBD. Since the initial pilot study, other research has shown similar findings of benefits of the LFD in IBD (Bodini et al 2019, Testa et al 2018). Similar to the LFD in IBS, it has also been suggested that the LFD be dietitian assisted, and only used short term (Pedersen et al 2017). In 2019, Bodini and colleagues found that in those with IBD, following a LFD was associated with an amelioration of fecal inflammatory markers. Shortly after in 2020, another study, specifically in people with ulcerative colitis, showed that consumption of a LFD might decrease systemic and intestinal inflammation (Milajerdi et al 2020). Similar to the concerns expressed for the use of the LFD in those with IBS, researchers in IBD suggested caution should be exercised due to the possible loss of prebiotic effects and nutritional adequacy (Colombel et al 2018, Halmos et al 2016).

Criticisms of the Low FODMAP Diet

Besides the aforementioned concerns of a LFD in both those with IBS and IBD, additional concerns have been mentioned. In a 2021 study by Weynants and colleagues, despite the fact that the long-term adherence and satisfaction of a LFD was high in patients with IBS, they indicated that it is difficult to follow. In one study, 64% of people thought the LFD diet was more expensive (Gearry et al 2009). Study participants reported that applying the LFD had negative impacts on their family and social life (Trott et al 2019). Following a LFD accentuated the participants sense of being excluded from communal events involving food and “such events needed to be navigated rather then enjoyed” (Trott et al 2019). Mari and colleagues (2018) showed greater adherence to a low-FODMAP diet is associated with eating disorder behaviour and suggest that in clinical practice it is important for a clinician to have a suspicion of eating disorders in IBS patients when a high level of LFD adherence is achieved.

Conclusion

The LFD has shown increasing evidence for use as short-term dietary treatment for those with IBS. Research has indicated that due to a number of concerns over nutritional adequacy, it

should be led by a qualified health professional, well versed in the intricacies of the LFD. Taking a probiotic while adhering to a LFD and ensuring proper reintroduction is done to liberalize the diet are suggested to counter some of the negative effects the diet can have on the colonic microbiota (Halmos et al 2015, Staudacher et al 2017). It seems that there is not yet enough robust evidence to support the use of the LFD long-term.

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The Health Benefits from Exposure to Green Spaces and Natural Environments

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Conflict of Interest

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The Health Benefits from Exposure to Green Spaces and Natural Environments

Abstract

Exposure to green spaces and natural environments is associated with a wide range of benefits to humans that touch on every major physiological system. A rapidly growing body of research has demonstrated improvements in cardiovascular health, immune function, stress response, inflammation, mental health outcomes, sleep quality, and cognitive function. Key research from the last 20 years is summarized here, with a discussion on possible mechanisms of action. While more rigorous research in the field is still needed, we expect the overwhelmingly positive associations that have been found thus far to be sufficient to confidently recommend regular exposure to natural environments to all urban dwellers.

Introduction

As a growing global population increasingly inhabits urban centers, humans find themselves living apart from natural spaces, both in distance and in lifestyle. Researchers have been turning their attention toward investigating nature's role in human health for several decades, with a marked acceleration in the past 15 years. Logan and Selhub released their book "Your Brain on Nature" in 2012 where they assembled scientific evidence around the psychological, social, and physical health benefits of nature, and advise physicians to recommend "Vitamin G", aka green space, to patients. Prior to that, it was author and researcher Richard Louv who garnered popular interest in this topic in 2005 and coined the name "Nature Deficit Disorder" to highlight the growing gap between people and nature. He postulates a theory called "The Nature Principle" and states that reconnection with the natural world is fundamental to human health and wellbeing (Louv 2005). These ideas of course are not novel. Most of us intuitively understand that connection to nature is linked with wellbeing, and literature and policy concerning this has been around for centuries (Hansen et al 2017). The Japanese in particular have understood this relationship well and their researchers have long been looking at the health effects of spending time in nature, or what they call "forest bathing" (Logan and Selhub 2012). More recently, these theories have been gaining a lot of support through a growing body of scientific evidence showing that the healing power of nature has measurable physical, psychological, and emotional effects. In many ways, the research is still new in the sense that there is still much heterogeneity, small sample sizes, and a lack of standardization. Nonetheless, there is now so much of it, that the collective results confidently support the conclusion that there is benefit to be derived from spending time in nature and increasing green spaces in cities. A 2018 systematic review and meta-analysis collected data on greenspace exposure and health outcomes, and the results show a wide range of beneficial effects; reduced cortisol levels, improved cardiovascular parameters (heart rate, blood pressure, heart rate variability, cholesterol), improvements in type II diabetes, reduced mortality (all-cause and cardiovascular), and better pregnancy outcomes (Twohig-

Bennett and Jones 2018). Another systematic review on forest bathing compiled studies that collectively show significant improvements in parameters relating to almost every body system, namely cardiovascular, hemodynamic, neuroendocrine, metabolic, immunity and inflammatory, antioxidant, electrophysiological, as well as improved emotional state and attitude, physical and psychological recovery, adaptive behaviors, anxiety and depression (Wen et al 2019).

Effects of Green Exercise

Physical activity is firmly established as a critical component of good health (Twohig-Bennett and Jones 2018). A systematic review published in 2011 concluded that there are additional benefits to mental and physical wellbeing resulting from exercising in nature (Coon et al 2011). The research team analyzed data from 11 randomized and non-randomized control trials comprising 833 adults. Eligible trials were those that compared the effects of outdoor exercise with indoor exercise and that reported physical or mental well-being outcomes. The review found improvement in mental wellbeing: increased energy and feelings of revitalization, and decreased tension, anger and depression compared with exercising indoors. Participants also reported greater enjoyment and satisfaction with outdoor activities (Coon et al 2011).

A 2010 meta-analysis by Barton and colleagues showed dose responses for duration of exposure to nature and intensity of exercise on the psychological parameters of mood and self-esteem. The greatest changes came from as few as five minutes of activity, thus suggesting that psychological parameters are immediately improved by green exercise. The benefits were lower for 10-60min of exposure, but rise again for whole-day duration. For intensity the greatest benefits are derived from either light activity or vigorous activity, but interestingly drop for moderate activity (Barton and Pretty 2010).

These studies, and many others, have collectively shown that green exercise can reduce stress, depression and blood pressure, increase self-esteem, mood and wellbeing, and enhance heart rate variability, in adults as well as children (Rogerson 2020 et al). These improvements can be felt after an acute bout of green exercise, or maintained over the long term, with regular doses of green exercise (Rogerson et al 2020).

Nature Exposure Reduces Cortisol Levels and the Stress Response

Chronically elevated cortisol levels are frequently seen in clinical practice. Stressful jobs, inadequate work-life balance, socioeconomic stressors, lack of sleep, and inadequate exercise are often the culprits. Cortisol is an important biological mediator of illness, and can play an important role in the progression of many diseases. A study by Vogelzangs and colleagues (2010) showed that high levels of cortisol measured in urine were associated with a dramatic increase in death from cardiovascular disease. Study participants with the highest levels were five times more likely to die from a heart attack or stroke than those with the lowest level. Since heart disease is the most common cause of death in North America, interventions that decrease risk are essential.

Several studies have looked at how salivary cortisol levels are affected by spending time in nature. The vast majority conclude that exposure to green spaces lowers salivary cortisol levels compared to pre-exposure baselines and controls, which is associated with reduced stress (Antonelli et al 2019, Hansen et al 2017, Li 2019, Twohig-Bennett and Jones 2018, Wen et al 2019).

A small but compelling Japanese cross-over study by Park and colleagues in 2007 demonstrated this effect. The researchers measured differences in salivary cortisol and prefrontal lobe activity between participants who spent a day in a forested area and those who spend the day in an urban area. When exposed to the natural setting, the participants not only had up to 50% lower levels of salivary cortisol compared to urban exposure, but also had significantly lower activation of the prefrontal cortex, which corresponds to their increased subjective ratings of comfort and calmness. Essentially, participants were feeling a lot less stressed and on “high-alert” when they were spending time in a natural setting. This can also be measured by assessing heart rate variability (HRV), with high frequency (HF) variability considered to be associated with parasympathetic nervous system activation and therefore lowered stress levels. Forest bathing has been shown to increase HF HRV (Hansen et al 2017).

A stress and cortisol reducing effect from green spaces can be achieved within cities as well. A study by Roe and colleagues (2013) found that exposure to natural green spaces within urban neighbourhoods resulted in healthier diurnal cortisol responses in middle-aged men and women from deprived urban environments, as well as reducing their perception of stress. This suggests that the dose of nature need not be massive to achieve the desired stress-reducing effect. Moreover, even gardening can have measurable stress reducing, and quality-of-life improving effects (Soga and Gaston 2016a, Van Den Berg and Custers 2011).

Nature Improves Cardiovascular Parameters and Reduces Risk

Cardiovascular disease and its risk factors are all too prevalent in primary care, therefore it is important to have a wide arsenal of recommendations. The research into cardiovascular benefits is somewhat more robust than for other body systems. Exposure to natural environments is associated with decreased heart rate, blood pressure, cholesterol, low frequency heart rate variability, stroke risk, CVD risk, and even cardiovascular mortality (Bhatnagar 2017, Gascon et al 2016, Li 2019, Tsunetsugu et al 2013, Twohig-Bennet and Jones 2018, Wen et al 2019, Yeager et al 2020).

Hypertension especially appears to be most susceptible to amelioration by nature exposure. The explanation as to why spending time in nature has such a reproducible effect on blood pressure is multi-factorial. It appears that there is an increase in parasympathetic nervous system activation, and a decrease in sympathetic activation, a decrease in cortisol levels, and an increase in subjective relaxation; all blood pressure reducing factors (Hansen et al 2017, Tsunetsugu et al 2013).

As an example, a research team out of China (Mao et al 2012) conducted a study to investigate the effect of natural spaces on cardiovascular biomarkers. Twenty-four comparable elderly participants with essential hypertension were divided into two groups, one group spent a day walking in the city, and the other in a national forest in similar, controlled manners. The team measured blood pressure, heart rate, and pulse pressure, as well as running assays to track any changes in interleukin-6 (IL6), tumor necrosis factor alpha (TNF-a), endothelin-1, homocysteine, renin, angiotensinogen (AGT), angiotensin II, angiotensin II type 1 receptor (AT1), and angiotensin II type 2 receptor (AT2). There were some significant differences between the two groups. Compared to the city group, those who walked in the forest had significantly lower blood pressure. Endothelin-1, homocysteine, AGT, AT1, and AT2 were also significantly lower in the forest group (Mao et al 2012). These serum factors are closely associated with essential hypertension. It is yet unclear if these kinds of effects are short-lived and limited to the time spent in nature or whether the changes endure. At the very least, it is very clear that a natural setting offers a respite for the cardiovascular system.

Nature Boosts Immune Activity

Stress hormones can compromise immune function by suppressing the action of natural killer (NK) cells (Li et al 2009). Evidence out of Asia is demonstrating that nature exposure increases NK cell activity (Li 2019, Wen et al 2019). This is believed to be partially due to evergreen trees, which secrete chemicals collectively known as phytoncides. Phytoncide is associated with improvements in human immune cell activity, particularly with enhancing human natural killer (NK) cell activity, the number of NK cells, intracellular anti-cancer proteins in lymphocytes, and significantly decreasing the concentrations of adrenaline and noradrenaline in urine (Li et al 2009). What's more, the increased NK activity measured in both blood and urine samples lasted for more than seven days after trips to forests in both male and female subjects (Li et al 2009). Nature exposure also seems to decrease cytokines TNF-alpha, IL-6 (Sarris et al 2019), and IL-8 (Wen et al 2019), for an overall anti-inflammatory effect.

Nature Exposure Improves Mental Health

Several studies have looked at urban "greenness" and how it relates to mental health. Gascon and colleagues published a systematic review on these studies in 2015, and found though the data quality is not high, the general trajectory of the effect is that nature exposure improves mental health parameters (Corazon et al 2019, Gascon et al 2015). As an example, one such study was a large cross-sectional population study out of Wisconsin (Beyer et al 2014). They controlled for a multitude of confounding factors, including demographic data, socio-economic status, and even level of health insurance and concluded that people living in greener neighbourhoods (as measured by percentage of tree canopy) had a decreased risk of depression and anxiety. More recent studies and systematic reviews continue to corroborate these findings: access to nature improves depression and anxiety scores, alleviates anger, increases relaxation, improves sleep

quality and quantity, and subjective well-being (Hansen et al 2017, Li 2019, Sarris et al 2019, Shin and Parab 2020, Wen et al 2019).

Living in a greener area seems to also improve mental health outcomes in the long run. A longitudinal study done by Alcock and colleagues (2014) showed that the mental health scores of people who moved to greener areas improved, while the scores of those who moved to less green areas deteriorated. Amongst those who moved to less green areas, the mean inverse score on the General Health Questionnaire fell from 10.15 to 9.99 right after the move, though it later rose back up, suggesting an accommodation to the new environment. No such accommodation was necessary amongst those who moved to greener areas. Their mean inverse scores rose progressively from 9.78 two years prior to the move, to 10.10 a year after the move to greener areas, and stayed there for the next two years, showing an improvement that was sustained.

Adding an outdoor component to typical interventions for mental health, such as cognitive-behavioral therapy (CBT), augmented the positive results of the intervention. Kim and colleagues (2009) undertook to compare the efficacy of CBT for major depression in hospital versus forest settings. They found that the participants who had undergone CBT in a natural setting had significantly lower depressions scores, and significantly higher remission rates. The added benefit effect is similar to what was found with outdoor versus indoor exercise. Horticultural therapy has a similar effect too. Substance abuse treatment program participants showed a trend for improvement in depression and an increase in quality of life when they combined horticultural therapy and occupational therapy, compared to just participating in the usual occupational therapy (Sarris et al 2019).

Nature Increases Cognitive Performance and Memory

Unsurprisingly at this point, some evidence suggests that nature exposure is beneficial to cognitive processes, such as working memory, cognitive flexibility, and attentional control (Stevenson et al 2018). In a 2003 trial by Hartig and colleagues, participants had to perform either a mentally taxing activity or a take a non-taxing drive to a field site. Each group was then divided and assigned to spend time in an urban environment or a natural one. The researchers measured blood pressure, affect, and performance on a memory test. The participants that got to recover in the natural setting, regardless of the initial task, had a faster decrease in blood pressure, and better performance on the memory test. Berman and colleagues (2008) did a similar study, and suggest that the reason for improved cognitive recovery in natural settings is that nature is less psychologically demanding and invokes a state of peacefulness. An urban setting demands more attention that in turn is cognitively taxing.

Nature Exposure for Children

The health of children has changed with the proliferation of urban living as much as it has for adults. Children spend increasingly more time indoors, with much of their time occupied by technology, even in school. It has been established that children’s development is enriched

through contact with nature, as they have greater opportunities to be creative, curious, take risks, strengthen their sense of self, and recover from stress (Dadvand et al 2017). All of these constructs contribute to positive psychological, emotional, motor, and cognitive development (Soga and Gaston 2016a).

Generally, studies evaluating the effect of nature on children's mental and cognitive health have been rather heterogeneous, with variable data, though the majority do show benefit (Balseviciene et al 2014, Gascon et al 2015). One study explored the potential use of 'green space play' to improve symptoms of ADHD. Parents of children diagnosed with ADHD were surveyed with a specially designed questionnaire. They were asked about their kids' attention and behaviour symptoms following play in various settings and asked to rank which type of play resulted in the best and worst overall behaviour: a green setting (eg. fishing, soccer), an ambiguous setting (eg. rollerblading, playing outside), or a non-green setting (eg. video games). The findings showed that green play significantly reduced ADHD symptoms when compared to non-green play (Taylor et al 2001).

There is evidence that nature's positive influence extends to babies in utero. Closer maternal proximity to green spaces was associated with significantly higher weight at birth, and reduced risk of low birth weight (Agay-Shay et al 2014).

Discussion

Research into the field of green spaces and nature exposure is being conducted globally, with positive associations between natural environments and human health being clearly identified. While the quantity of the data has increased, often the quality of individual studies is low. Much of the existing research is cross-sectional, observational, susceptible to socioeconomic confounders, or conducted with small sample sizes. Nonetheless, there is something to be said for the fact that the overwhelming majority of the evidence shows a positive relationship between biomarkers of health and nature exposure. Collectively, these studies confirm that being in contact with nature can reduce psychological and physical stress, improve cardiovascular risk factors, benefit adult's and children's mental health, reduce inflammation, boost immune function, improve antioxidant capacity, sharpen cognition, improve sleep quality, and very simply increase feelings of wellbeing.

Quite a bit of thought has been given to try and understand why such effects exist, and why it is that human beings seemingly require this connection to nature for good health. Two of these are Kaplan and Kaplan's attention restoration theory, and Ulrich's stress recovery theory (Bowler et al 2010, Twohig-Bennett and Jones 2018). Attention restoration postulates that natural environments provide specific stimuli that allow our cognitive attention capacity to recover from the rigors of urban life, by providing a break from our routine stresses, and allowing a 'soft fascination' with the environment which is not taxing on our minds. Stress recovery is a complementary theory that suggests that natural features trigger an evolutionary adaptive response that generates feelings of positive affect, safety, and survival. Both of these theories

suggest that there is something about viewing features of the environment that triggers healthy responses, and some evidence suggests that it is indeed visual stimuli which play a large role. When study participants viewed virtual images of natural landscapes (computers or VR setups), they demonstrated reduced stress and increased relaxation and wellbeing compared to images of urban landscapes, or indoor settings (Browning et al 2020, Zabini et al 2020). In another study, functional MRI was used to compare brain activation when viewing images of natural and urban landscapes. It was found that Brodmann area 31 was activated only with natural images, which is associated with adjusting attention (Tang et al 2017).

Other mechanisms of how nature exposure promotes human health include the increased opportunity for physical activity, opportunity for social interaction, exposure to sunlight and vitamin D, exposure to negative ions, phytoncides, and volatile oils, and exposure to the kinds of symbiotic microorganisms that humans have evolved with (Twohig-Bennett and Jones 2018). Exposure to natural environments has been associated with higher gut microbial biodiversity, which is associated with improved immune maturation and reduced risk of immune diseases and disorders (Tasnim et al 2017). This is not seen with urban environments. In fact, urban environments are associated with health-harming factors, such as poor diets, pollution, sedentary lifestyles, and social and psychological stress (Soga et al 2016b). Humans have evolved for centuries within natural environments. If natural features are removed from the human experience, mental and physical health suffers. Take for example the data that shows that immense loss of trees from the emerald ash borer infestation in the northern US is associated with a small but significant increase in CVD and respiratory deaths in those areas (Bhatnagar 2017).

The kind of evidence discussed here hopefully makes it easy for all types of health care practitioners to begin recommending nature exposure to their patients if they aren't already. Forests and other undeveloped areas would be most ideal, but they are not accessible to everyone. Gardening is an easy prescription for exposure to green spaces (Soga et al 2016b), which can be accessed in rural and urban areas (as private plots, container/balcony gardens, or community gardens). Urban dwellers from many socioeconomic backgrounds can find health benefits since urban parks are also effective. In the absence of urban parks, or where accessibility to them is restricted or difficult, even virtual exposure can offer some mental health support (Browning et al 2020).

Conclusion

Naturopathic medicine originated in the 'nature cure' traditions of European healers, to whom spending time in nature was an integral part of providing natural health care. Cultures all over the world have long recognized the importance of closeness to nature. Many of these traditions have been preserved, or are undergoing a rebirth, such as the forest bathing practices in Japan, where they have established Forest Medicine as a new interdisciplinary science (Li 2019). Certainly, naturopathic medical philosophy maintains this connection as well. However, our

modern lives have led to a distancing from nature, and all of us are likely sensing the rift. The evidence that has been summarized here highlights the important health benefits that result from being in touch with natural spaces.

Having established the varied and important ways in which exposure to nature can benefit humanity, it now becomes imperative that research in this field moves to establish high quality data through standardization of methodology and greater scientific rigor. It is this level of evidence that is most likely to influence and guide policy and urban planning to adequately incorporate natural environments within cities (Nieuwenhuijsen et al 2017). In the meantime, considering especially that the level of risk is very low relative to benefit, we recommend that "Vitamin G" should make its way back to the prescription pads of every healthcare provider, particularly for those patients living in urban environments.

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Physical, Cognitive, and Social Impacts of Video Games in an Elderly Population

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Conflict of Interest

The Author declares no conflicts of interest.

Physical, Cognitive, and Social Impacts of Video Games in an Elderly Population

Abstract

The health of the elderly population is becoming increasingly more important as people are living longer and the aging population is growing. Video games can provide an engaging method through which participants can potentially expand and maintain their cognitive skills as well as their physical capabilities, such as mobility, strength, balance, and coordination. Additionally, video games may serve as a means to promote social interaction and develop a sense of belonging. However, video games are a remarkably diverse medium, and the question of which game provides the most therapeutic benefit for cognitive, physical or mental health decline remains to be answered. This review will explore several recent game-based interventions and discuss this impact on cognitive, physical, and social well being.

Introduction

The elderly is a growing demographic and is expected to double by the year 2050 (Kanasi et al 2016). With this increase in aging population comes the expected increase in strokes, neurodegenerative conditions such as dementia's, and Parkinson's disease, as well as increase in mental health decline associated with loneliness due to loss of social contact and isolation. Numerous physical rehabilitation and community programs have been developed to provide both cognitive, physical, and social stimulation to this target population. However, with limited access to rehabilitation and exercise programs during the COVID-19 lockdown in many parts of the world, as well as mandated social distancing, the use of video games to provide therapeutic benefit becomes more relevant. Given the diversity of the virtual reality and gaming worlds, it is not clear what type of game is best suited for which population and patient group. This review will explore the current research available on a range of video games and summarize their benefits, limitations, and potential applications.

Currently, the majority of studies are exploring the value of exergames. Exergames are video games that integrate physical exercise into the virtual reality of the game by the use of motion sensing equipment. These include Nintendo Wii games, such as Wii Sports; tennis, golf, bowling and others, and Wii Fit, such as yoga and balance training as well as Microsoft Xbox Kinect games. By definition, exergames do not have to have a 'serious' or therapeutic component, however, many of the games are hypothesized to provide both cognitive and physical benefits in an entertaining and motivational way. Additional applications to be discussed here include game-based neurofeedback and the use of 'whack-a-mole' game as a form of cognitive assessment.

All of the studies reviewed here explore the therapeutic benefit of games on either healthy elderly populations or participants with various neurological disorders. The neurological

disorders include dementia, Alzheimer's Disease (AD), Parkinson's disease (PD), post-stroke recovery, mild cognitive impairment (MCI), and Multiple Sclerosis (MS).

Physical Impact

A randomized control trial of 32 healthy elderly participants (ages 65 – 78) compared the physical benefits of exergames to a sedentary lifestyle (Maillot et al 2012). The exergames included Nintendo Wii Sports, Wii Fit, Mario & Sonic on Olympic Games and were played for one hour twice per week for 12 weeks, in pairs to increase the enjoyment aspect of the game. Not surprisingly, these games resulted in statistically significant improvements in physical measurements such as six-minute walk, chair stands, arm curls and average heart rate at the end of a six min walk ($p<0.001$). However, the exergames also benefited cognitive function demonstrating significant improvements in processing speed ($p<0.001$) and executive function ($p<0.001$), while no improvements were seen with visuospatial function. The authors suggest that these cognitive improvements were due to improved oxygen transport and utilization provided by the aerobic component of these exergames. It is unclear if the cognitive improvements were dependent on the physical achievements or if they were related to the social impact provided by the partner involved in the exergame.

To determine whether exergames can provide motor benefits to participants with mobility issues de Melo Cerqueira and colleagues (2020) compared the effects of Kinect based exergames on participants with PD versus healthy elderly in physical and cognitive outcomes. The Microsoft Kinect games included Paddle Panic (simulation of table tennis), Wall Break (requiring kicking), Bump Basin (requiring side stepping) and others. Each session was 45-60 minutes long and there were 10 sessions completed over the course of five weeks. While there were no statistically significant improvements in motor outcomes compared to baseline, including Berg Balance Scale, Timed Up and Go and the 10 Meter Walk Test in either of the two groups, there was significant improvement in the Montreal Cognitive Assessment (MoCA) ($p<0.05$) compared to baseline in both groups of participants. Additionally, there were significant improvements in the Frontal Assessment Battery in both groups ($p<0.05$), but these gains were lost in the group with PD at the 30 day follow up, while they were maintained by the healthy elderly.

Another study examining the effects of exergames on motor function of participants with PD is a small observation study by Severiano and colleagues (2018). In this study, participants (n=16) had access to various exergames that worked with Nintendo Wii Balance Board, including Soccer Heading, Tablet Tilt, Tight Rope Walk and Ski Slalom. The participants engaged in these for 50 minutes twice per week for a total of 20 sessions. Significant improvements compared to baseline were observed in Dizziness Handicap Inventory ($p=0.001$), Sitting-Rising Test ($p=0.0222$), and Berg Balance Scale ($p=0.03$), with the later being correlated to reduced risk of falling, which is particularly significant with this condition. One distinguishing feature of this study compared to that of de Melo Cerqueira and colleagues (2020) is the use of the Wii Balance Board that can pick up subtle changes in the shift in weight, as opposed to a sensor position one

meter away from the participant that was used in the later study. This sensor can detect changes in movement but is likely to miss the subtle shifts in weight that may be immeasurable from this distance and thus less likely to provide this feedback to the participant, which can explain the lack of benefit in balance reported by de Melo Cerquiera and colleagues (2020).

A recent randomized control trial by Kannan and colleagues (2019) examined the effect of exergame on the physical and cognitive function of participants recovering from stroke (n=25). All participants were able to stand independently for five minutes and had suffered the stroke more than six months ago but were experiencing some hemiparesis. The exergames combined both balance and coordination physical training with various language, memory, and mathematical skills training using Nintendo Wii Fit (such as Bubble Balance, Table Tilt, Tight-Rope Walking, and others), while the conventional training group included stretching, strengthening, balance and endurance training without any cognitive training. There were 10 90-minute sessions completed over the course of six weeks. There were significant improvements in balance ($p<0.05$) in both exergame and conventional training groups compared to baseline, and significant improvements in cognitive function compared to conventional training, which was measured using Letter-Number Sequencing task that measures verbal working memory ($p<0.01$). While this study demonstrates capacity to improve balance without the use of the Wii Balance Board, it is difficult to make strong conclusions since the method to assess balance were different between the Kannan and colleagues (2019) and Severiano and colleagues (2018) studies. However, from the four studies discussed here it is clear that some cognitive benefit can be achieved through exergames. The next set of meta-analyses will explore the question of potential cognitive improvements in more detail.

Cognitive Impact

Stanmore and colleagues (2017) completed a meta-analysis of 17 randomized controlled trials with a total of 926 participants. Participants included healthy elderly adults as well as those with neurocognitive impairments such as MCI, sub-acute stroke, schizophrenia, and PD, though the majority of the studies were exclusive to healthy adults. On average the exergame sessions ran for 15-60 minutes 3.2 times per week for 10 weeks. Outcomes included significant improvement in global cognition and executive functions, such as inhibitory control and task-switching flexibility as compared to wait list control groups and physical exercise interventions. Stanmore and colleagues (2017) concluded that exergames provide greater benefit for cognitive function than physical exercise alone, but do not outperform cognitive training interventions. This statement is echoed by a more recent review paper by Sokolov and colleagues (2020), which reports improvement in executive function, attention, and visuospatial processing by both healthy elderly and those with mild cognitive impairment. Sokolov's work suggests that outperforming physical exercise is not a consistent pattern seen with exergames, though the researchers agree that exergames increase the likelihood of participants adhering to physical exercise required within the game.

Another meta-analysis of 13 control studies (including eight randomized control trials) explored the benefits of exergames on cognitive function of individuals with various neurological disorders (Mura et all 2018). The participants included those recovering from stroke, and those suffering with MS, PD, dyslexia, MCI, and those diagnosed with Down's syndrome. The interventions relied on Nintendo Wii Sports and Wii Fit, while the alternative comparison ranged widely from occupational therapy, simple walking, computer-assisted cognitive training, group, or individual balance training, wait list and others. The sessions also differed in frequency and duration ranging from 30-90 minutes one to five times per week for two to 24 weeks. The analysis demonstrated significant improvement in visuospatial perception ($p<0.001$; 5 studies), and executive function ($p<0.005$; 8 studies), but no significant improvement in attention and global cognitive function compared to the alternative. Mixed results were obtained with respect to follow up with two studies reporting loss of benefit after intervention ended, while three studies demonstrated preserved benefit on executive function in participants with PD and stroke. The authors also highlight the importance of adherence to the intervention and share a quote from one of the participants, "…they looked forward to play the next session and came to therapy more willingly in order to improve their scores". While the intrinsic benefit derived from physical or cognitive exercise seems to be incredibly important, the extrinsic reward of an 'improved score' appears to be more motivating.

A recent randomized controlled trial by Karssemeijer and colleagues (2019), which was not included in the earlier meta-analyses, compared the cognitive effects of exergames versus aerobic exercise to control (no intervention) in participants with dementia. The exergame required participants to navigate a virtual reality on a stationary bicycle. In addition to the navigational component, participants had to engage in other cognitive tasks that targeted processing speed, task switching and response inhibition. The aerobic exercise was limited to cycling on a stationary bike, while the control group did not engage in any exercise at all. The sessions ranged from 30-50 minutes and occurred three times per week for 12 weeks. The outcomes were assessed at baseline, at the end of the study and at the 12 weeks follow up. Both types of training were considered light as they hovered at an average of 42% of maximum heart rate. There was no significant difference between either training group in executive function, episodic memory or working memory compared to control. The only significant improvement was in psychomotor speed ($p=0.007$ for aerobic training and $p=0.009$ for exergame), which was maintained at the 12-week follow up. As can be seen from these reviews and clinical trial, exergames are not created equally and effect different aspects of cognitive function, though in most cases there are improvements with executive function and visuospatial perception.

Social Impact

As the COVID 19 virus forced citizens of various countries into quarantine, social isolation has become an obvious complication. Social isolation is an important driving force in experience of loneliness, which has been correlated with numerous health detriments including dementia and depression (Sundström et al 2020). Gabbiadini and colleagues (2020) set out to examine the

effect of technology, including video games, on the perception of loneliness and belonging. This observation study took place in Italy during the March 2020 lock-down where participants were required to stay inside for several weeks without physical contact with anyone outside the household. Using a questionnaire, the researchers assessed the degree to which participants engaged in various technological communication tools including video calls, streaming movies in party mode, playing online board games and online multiple video games, and compared this to their results of various psychosocial assessment such as the UCLA Loneliness Scale-Revised, Brief Irritability Test, State-Trait Anger Expression Inventory, and others. Not surprisingly, connecting with others through various technological means correlated positively with a sense of belongingness and negatively with feelings of loneliness, boredom, anger, and irritability. However, as the study did not separate the type of technology that was being used, these results cannot be specifically applied to the video games alone.

To explore the impact of exergames on the experience of loneliness, Li and colleagues (2018) conducted a systematic review of 10 clinical trials. The studies incorporated exergames from Nintendo Wii Sports, such as tennis, bowling, golf, basketball and boxing, Nintendo Fit package, such as yoga and balance games, as well as various exergames by Microsoft Xbox Kinect. The majority of the studies provided 40 min sessions at two to three sessions per week for six-12 weeks. The studies compared these exergames to traditional board games as well as group experiences like watching TV. Despite the fact that both traditional board games and watching TV were group activities, exergames proved to be more engaging and provided the participants with a greater sense of connection as illustrated by reduced loneliness perception. Perhaps being physically active together is an important variable in reducing the sense of loneliness or being physically active helps to raise the mood more than could be accomplished with an enjoyable but sedentary activity like traditional board games, and greater mood could reduce perception of loneliness.

Additional Applications

Game-based neurofeedback (NFT) incorporates the use of commercial grade electroencephalogram (EEG) into the design of the game, whereby the EEG becomes the joystick. The participant must alter their brain waves by engaging in specific cognitive skills in order to accomplish specific game tasks. Jirayucharoensak and colleagues (2019) designed a randomized control trial with 65 women with MCI and 54 healthy elderly women and compared the impact of NFT, exergame and regular lifestyle on cognition. The participants in NFT and exergame groups completed a total of 20 sessions, each session was 20 minutes, and were assessed before and right after the completion of the study. During the game, the participant is required to maintain their focus and attention on a particular component. An example of this game would be where a participant is required to focus on a bear on the computer screen. If the patient is successful at maintaining attention, as assessed using the EEG, the game provides this feedback to the participant by having the bear run faster. Once the attention is lost and the participant is distracted, the EEG signals this to the game and the participant receives feedback

by observing the bear slow down. The NFT demonstrated significant improvement (compared to exergame and control) not only in sustained visual attention, which was the target skill, but also in working memory. These improvements occurred in both healthy and MCI groups.

Another interesting way to apply games is in the field of screening and monitoring. Wilkinson and colleagues (2018) demonstrated the potential for using a video game in the emergency department to identify patients with significant cognitive deficiencies. The group compared the score of "whack-a-mole" video game to validated cognitive assessments such as the MMSE and MoCA and were able to correlate the poor score with these assessments. They argue that this type of game assessment could be generalized to other healthcare settings, including long-term healthcare facilities where these games could be used to monitor for progression, treatment response and/or identify acute changes that would otherwise take longer to recognize. On the topic of long-term healthcare facilities, this research team also reported on the testing of the application of ambient activity wall unit (ABBY). ABBY is not a video game, but an interactive technology designed to engage patients with dementia with sensory interactive content that has been populated with media content selected for the specific individual patient. This technology is made to be accessible completely without any support from staff at all times (24/7). After three months, the patients (n=27) demonstrated statistically significant reduction in physical and verbal agitation, paranoia, delusions, aggressiveness, and anxiety and increase in quality of life. While the ABBY did not have any cognitive training built into the interface, and differences observed did not reach statistically significance, it did trend towards cognitive improvement (p=0.080). Furthermore, there was an added benefit of this technology in that staff experienced a significant decrease in burn-out after one months of having patients interact with ABBY.

General Benefits and Limitations

There is limited discussion of the potential safety issues surrounding exergames and regular video games. The studies were careful to either exclude patients with severe mobility problems that would be at risk of falling or provided a physiotherapist as a supervisor to ensure safety. With these provisions in place, there were no adverse events reported in any of the studies reviewed here, except for one.

West and colleagues (2018) report reduction in the size of the hippocampus after engagement with first person shooting games. These games require the participant to engage in navigational strategies to proceed through the game. Two navigational strategies that were discussed included spatial strategy – "spontaneously encod-[ing] the relationship between landmarks" and non-spatial strategy where the participant memorized a sequence of events and used this information to navigate throughout the game. The study utilized an MRI to analyze the baseline characteristics of the participants and the impact that these games had on their neuroanatomy. They discovered that participants with reduced hippocampus were often engaging in non-spatial navigational strategies, which do not require the use of the hippocampus and were most likely to suffer from further loss of grey matter within their hippocampus after engaging in these games.

Participants who employed spatial-based navigational strategies used their hippocampus more during the game and thus did not suffer the loss of the associated grey matter. This finding, while alarming, can help to explain the discrepancies seen in the cognitive benefits from video games. While most of the research examines the differences between video games in their design and their posology, this study highlights the importance of comparing the participants according to their game strategies and neuroanatomy, suggesting that the same game can have vastly different outcomes on their neuroplasticity and subsequent cognitive outcomes.

In addition to the potential physical, cognitive, and social benefits already discussed prior, there were several other important features reported by the researchers in the studies reviewed here. Several studies commented on the enjoyment and fun entertainment provided by the video games (Li et al 2017, Mura et al 2018). This enjoyment serves as a motivator to engage in physical exercise through exergames. Since adherence to exercise is often limited by lack of desirability of this activity, finding ways to increase compliance is important especially in a population often suffering from mood disorders. Another relevant benefit is that the majority of the commercial exergames can be accessed at home. This increases participation for patients with mobility issues that find travel difficult, as well as allows engagement during lockdowns. These games are also relatively more affordable than some of the exercise and sports programs.

The diversity across video games allows for this intervention to cater to a wide range of interests and range of cognitive and physical capabilities. For example, patients with limited lower leg mobility that are confined to a wheelchair can still engage in the exergames that target upper body strength and reap the cognitive benefits associated with the challenge that these games provide. Lastly, these games do not have to be played alone, which can increase their enjoyment and benefit.

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Metformin and Cancer – Is There Value for the Non-Diabetic Patient?

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Conflict of Interest

The Author declares no conflicts of interest.

Metformin and Cancer – Is There Value for the Non-Diabetic Patient?

ABSTRACT

Observational studies of metformin use among individuals with diabetes suggest an anti-cancer effect of this drug. Its effects, if any, in a cancer-affected but non-diabetic population are uncertain. A literature review was conducted. Twenty-three clinical trials and one case report were identified. Metformin use was associated with improved clinical presentation in precancerous conditions including aberrant crypt foci, adenomas and dysplasia. In patients with invasive cancers, metformin decreased the proliferation marker Ki-67. This effect was enhanced in some studies by stratification of patients by hormone receptor status, human epidermal growth factor receptor 2 status, body mass index and insulin responsiveness. Weight, insulin resistance and fasting blood glucose were all improved under metformin treatment. Concerning cancer-related outcomes, studies of progression-free, disease-free and overall survival have yielded inconclusive results. Some benefit was demonstrated in colorectal, prostate, ovarian, and endometrial cancers with mixed results in breast and lung cancers, and neutral results in pancreatic cancer. Future prospective research should explore the use of metformin in both diabetic and non-diabetic individuals to hone the utility of this agent in the context of cancer-related outcomes.

INTRODUCTION

Metformin has been the mainstay of diabetic treatment for almost 100 years (Ahmed et al 2021). This biguanide is generally well-tolerated (Nasri and Rafieian-Kopaei 2014), with a side effect profile that can include gastrointestinal disturbances and, rarely, lactic acidosis. For many diabetic patients, this medication is taken for prolonged periods until it is no longer effective or until adverse effects necessitate a change in medication.

Individuals with a diagnosis of diabetes are at higher risk of subsequently developing cancer (Ling et al 2021). This fact may be explained in part by significant overlap in the risk factors for both cancer and diabetes, which include obesity, a sedentary lifestyle, dietary factors, and high blood levels of insulin and glucose (Jee et al 2005).

In 2005, Evans published a study that would intertwine cancer and diabetes from that point forward. This report put forth the notion that metformin may not only manage diabetes but could reduce the risk of developing various cancers.

In the sixteen years that have elapsed since the publication of this pivotal study, a flurry of research has explored the nature of the relationship between metformin, cancer risk and cancer outcomes. This paper seeks to describe the current evidence for this association, focusing on

prospective trials in non-diabetic patients to evaluate a potential anti-cancer effect in this population.

METHODS

Searches were conducted in PubMed in February and March of 2021. Results were screened and limited to human trials and case reports investigating metformin use in non-diabetic individuals diagnosed with a cancerous or pre-cancerous condition.

Observational studies, both prospective and retrospective, were incidentally reviewed during screening. These publications evaluated the impact of metformin use among patients with diabetes upon cancer-related outcomes. As metformin use has historically been restricted to diabetic individuals, no observational studies of metformin use in non-diabetic patients were identified.

RESULTS

A total of twenty-three clinical trials and one case series pertaining to non-diabetic individuals were identified.

Premalignant Conditions

Four papers discussed the impact of metformin use in precancerous conditions, with a fifth (DeCensi et al 2015) commenting upon precancerous lesions found adjacent to invasive cancer. Diagnoses included aberrant crypt foci (ACFs), ductal carcinoma in situ (DCIS), colonic adenomas and dysplastic lesions associated with head and neck cancers.

Benefit was seen in two controlled trials that reported significant reductions in the number or risk of ACFs, adenomas and polyps following treatment with metformin (Higurashi et al 2016, Hosono et al 2010). A third study assessed effects on the proliferation marker Ki-67 and is described below (DeCensi et al 2015). Conversely, a single-arm study found no benefit from 12 weeks of 2000mg of metformin on this same marker of proliferation (Zell et al 2020).

A single case series was included and described three patients given metformin to treat dysplastic lesions. These patients, with histories of oral or laryngeal cancer, all experienced partial or complete responses to metformin and required no further surgical intervention (Lerner et al 2017).

Invasive Cancers

The remaining 20 publications evaluated individuals with a diagnosis of invasive cancer and examined changes in metabolic, biological and clinical outcomes.

Metabolic Parameters

In patients with diabetes, metformin improves insulin sensitization (Lange et al 2021), reduces blood glucose, and decreases body mass (Attiya 2020). Similar effects are noted in a non-diabetic population taking metformin.

Among non-diabetic patients, five of six studies reporting on metabolic parameters found statistically significant improvements in plasma insulin, insulin-like growth factor 1, IGF binding protein 7, body mass index (BMI), weight, the homeostatic model assessment of insulin resistance (HOMA-IR), fasting blood glucose (FBG) and cholesterol (El-Haggar et al 2016, Kalinsky et al 2014, Laskov et al 2014, Niraula et al 2012, Rothermundt et al 2014). Only one study (Petschsila et al 2020) showed no significant change in metabolic parameters.

Ki-67 Index/Labeling Index

Ki-67 is a marker of proliferation that has been investigated for its utility as a prognostic indicator of pathological complete response to treatment (pCR) (Fasching et al 2011). Nine included publications reviewed the effect of metformin treatment on Ki-67. These studies included women with breast or endometrial cancer and compared Ki-67 results from biopsy samples to those from tumours retrieved from the same patients through surgery at a later date. Metformin was administered from time of diagnosis through to the day before or the day of surgery.

With the exception of three studies (Bonanni et al 2012, Cazzaniga et al 2013, Kalinsky et al 2014) statistically significant decreases in Ki-67 were universally identified (DeCensi et al 2014, DeCensi et al 2015, Hadad et al 2015, Laskov et al 2014, Niraula et al 2012, Petchsila et al 2020). An interaction between estrogen receptor (ER) status and human epidermal growth factor receptor 2 status (Her2) was reported by DeCensi and colleagues (2015), as the decrease in Ki-67 was only significant in women with ER+/Her2+ disease. Results in ER- or Her2-disease were non-significant.

An earlier publication by the same team (DeCensi et al 2014) reported a similar interaction with ER+ disease and Ki-67 percentages. Additionally, this group noted a parallel effect in women who were insulin resistant (HOMA-IR >2.8) or had elevated inflammatory markers (highly sensitive C-reactive protein (hs-CRP)). Other groups reported that changes in Ki-67 LI were independent of BMI (Hadad et al 2015), FBG and hemoglobin A1c (Petschsila et al 2020).

AMP-Activated Protein Kinase (AMPK) and Cancer Stem Cells (CSCs)

AMPK is a regulator of energy homeostasis in the body (Choi and Park 2013). Metformin is believed to activate AMPK-mediated pathways, increasing fat oxidation in the liver and promoting hepatic insulin sensitivity (Rena et al 2017). In addition, AMPK may have anti-proliferative effects in the context of cancer (Choi and Park 2013).

Two trials examined the effects of metformin therapy on AMPK levels, and both identified an increase in the studied population (Godara et al 2020, Hadad et al 2015), suggesting an activation of this kinase by metformin in non-diabetic patients. One paper (Godara et al 2020) described an association between increased AMPK levels and stable disease, but statistical significance was not reported.

Cancer stem cells (CSCs), thought to play an essential role in the initiation of cancer and the development of treatment resistance (Zhang et al 2021), may be a further target of metformin treatment. Brown and colleagues (2020) report decreases in ovarian CSCs compared to tumour samples from historical controls following 24 weeks of treatment with metformin. This decrease was further associated with survival that was "better than expected" when compared to historical controls.

Adverse Effects of Treatment

Metformin has also been investigated for its impact on adverse effects experienced by patients undergoing treatment for cancer. Patients receiving concurrent metformin and chemotherapy had less nausea (Sayed et al 2015) and fewer high-grade incidents of neutropenia (Nanni et al 2019) than their counterparts in control groups. Conversely, individuals receiving a tyrosine kinase inhibitor (TKI) alongside metformin reported more diarrhea with the combination than without (Li et al 2019).

Outcomes Relating to Disease Progression and Survival

Survival outcomes are undoubtedly the most desirable yet elusive targets of treatment. Eleven studies investigated the association between metformin treatment and impacts on overall survival (OS), cancer-specific survival (CSS) and progression free survival (PFS), while one assessed prostate specific antigen (PSA) as a marker of disease progression. These publications included patients with cancers of the breast, digestive tract, prostate, lung and ovary with daily metformin doses ranging from 500-2000mg per day.

Positive Studies

Five papers report positive effects of metformin on survival outcomes and progression of disease. These included OS that was "better than expected" in an uncontrolled trial (Brown et al 2020), and a report of disease control in 55% of the treated sample in a crossover study (Godara et al 2020) (no p-value expressed). A second uncontrolled trial found a decrease in PSA and an increase in PSA doubling time (Rothermundt et al 2014), suggesting a possible impact of metformin on disease progression.

PFS was 47% in a randomized controlled trial (RCT) in patients with lung cancer treated with chemotherapy and metformin, compared to a PFS of 15% in a historical control group (Marrone et al 2018) – PFS was 9.6 months in the treatment arm and 6.7 months in the control arm ($p=0.024$). A second controlled trial found that metformin treatment was associated with improved PFS ($p=0.044$) and fewer metastatic events at six months ($p=0.05$) in women with breast cancer (El-Haggar et al 2016). This difference was no longer statistically significant at 12 months, owing perhaps to the small size of the study.

Neutral and Negative Studies

Three RCTs in patients with breast and lung cancers found no change in survival outcomes with metformin treatment (Pimentel et al 2019, Nanni et al 2019, Sayed et al 2015). The remaining three included trials, conducted in patients with advanced lung or pancreatic cancers, found non-

significant trends towards poorer outcomes with the combination of metformin with a TKI or chemotherapy (Kordes et al 2015, Li et al 2019, Reni et al 2016).

DISCUSSION

Hundreds of observational studies have investigated the link between metformin use among individuals with diabetes and cancer-related outcomes since the association was first described in the literature (Evans et al 2005). Systematic reviews summarizing the outcomes of these studies generally report the following:

- Metformin use in patients with diabetes may be associated with lower rates of cancer incidence (Ng et al 2020).
- Metformin may be associated with improved OS and PFS in those with diabetes and cancer (Cao et al 2017).

These positive effects are not seen in every study (Danker et al 2019) or even in every systematic review (Hevroni et al 2020), and some authors wisely advise caution in interpreting the results of these studies for prospective application (Gandini et al 2014).

Treatment by Cancer Site

One important question that results from this somewhat inconclusive research is whether there are cancer sites that are more susceptible to metformin therapy than others. Prospective trial data is discussed below by cancer site.

Colorectal Cancer

Studies in colorectal cancer and its precursors were among those to report the most consistent benefit. As described above, trials in patients with previous ACFs and colonic adenomas experienced clinical regression of their conditions with metformin therapy (Higurashi et al 2016, Hosono et al 2010). Disease stabilization was seen in 55% of participants with invasive gastrointestinal cancers in a later study (Godara et al 2020). More than half of the participants in this crossover trial had colorectal cancer.

These few studies seem to suggest a possible role for metformin in the management of colorectal cancer in non-diabetic patients. This impression is supported by a 2021 practice guideline released by the American Gastroenterological Association, encouraging the use of metformin for its possible anti-neoplastic effects in patients with diabetes (Liang et al 2021).

Encouraging Trends – Ovarian, Endometrial and Prostate Cancer

With such a limited pool of trial data, it is impossible to draw clear conclusions regarding the disease sites that are most susceptible to any anti-cancer impacts of metformin. However, promising results were seen in:

- Ovarian cancer, where a decrease in the number of CSCs was noted, alongside improved overall survival compared to historical controls (Brown et al 2020).

- Endometrial cancer, where decreases in proliferation markers and improvements in metabolic parameters were demonstrated (Laskov et al 2014, Petschsila et al 2020).
- Prostate cancer, where the single uncontrolled trial reported decreased PSA activity in advanced and metastatic disease (Rothermundt et al 2014).

Mixed Results – Breast and Lung Cancer

Clinical trials in breast cancer principally evaluated the effects of metformin on Ki-67, BMI, and insulin resistance. Of the studies assessing survival outcomes, one study found very encouraging reductions in metastatic spread six months after the initiation of hormone therapy. Unfortunately, these differences were not statistically significant by the 12-month time point, somewhat complicating interpretation (El-Haggar et al 2016). Other authors reported no measurable effect in PFS, OS or risk of recurrence (Nanni et al 2019, Pimentel et al 2019).

Studies in lung cancer offer equally contradictory results, with one trial presenting remarkable outcomes – a tripling in the rate of PFS at one year compared to historical controls (Marrone et al 2018) – and the other finding no significant between-group-differences in PFS or OS (Li et al 2019). Larger studies are certainly required to evaluate the significance of these findings.

Neutral Studies – Pancreatic Cancer

The two clinical trials in pancreatic cancer may present a more cohesive, albeit negative picture (Kordes et al 2015, Reni et al 2016). These placebo-controlled trials, both using 2000 mg/day of metformin, showed no evidence of benefit in either PFS or OS and in fact, resulted in non-significant trends to poorer outcomes in the treatment group. While their outcomes may align neatly, it is impossible to make a clinical judgment on the strength of two studies. Further efforts to understand the ideal sites of metformin action are urgently required.

Impact of Disease Stage

Stage of disease may impact outcomes from metformin therapy, suggesting that later stage and metastatic disease may not respond to treatment (Li et al 2017). Results from Sayed's 2015 trial in metastatic lung cancer and the controlled trials in pancreatic cancer (Kordes et al 2015, Reni et al 2016) corroborate this perspective. This is further supported by the benefits reported in precancerous conditions (Higurashi et al 2016, Hosono et al 2010, Lerner et al 2017), suggesting optimal effect in earlier stages of disease.

However, positive outcomes have been documented in patients with advanced disease as well. Over 52% of metformin-treated patients with metastatic prostate cancer had prolonged PSA doubling time in one uncontrolled trial (Rothermundt et al 2014), while 47% of people with advanced or metastatic lung cancer (Marrone et al 2018) were progression-free at 1 year, compared to the expected 15% suggested by historical controls. These inconsistencies present other key opportunities for further research.

Effects by Patient and Cancer Characteristics

Alongside disease stage, patient characteristics such as BMI, insulin resistance and inflammation as well as tumour receptor status may profoundly impact interpretation of results. This is

demonstrated in three publications on the same group of 200 women receiving metformin between biopsy and surgery for breast cancer.

The initial publication (Nanni et al 2012) reported no significant change in Ki-67 with metformin treatment but when patients were stratified by characteristic, significant changes were seen in women with ER+/Her2+ disease (DeCensi et al 2015) or inflammation and insulin resistance (DeCensi et al 2014). This knowledge may help tailor metformin trials and treatment to those who may be expected to derive the most benefit from it.

Impact of Metformin on Risk Factors and Mechanism of Action

Obesity, insulin resistance (Jee et al 2005) and elevated fasting blood glucose levels (Haseen et al 2015) have all been associated with an increase in cancer risk. Although patients in these studies were not classified as having diabetes, participants with metabolic risk factors were included.

With the exception of one paper, metformin consistently and significantly modified these risk factors. It is notable that the neutral trial (Petchsila et al 2020) used metformin for as little as 12 days at the relatively low dose of 850 mg per day. These effects suggest that metformin improves metabolic parameters in non-diabetic people and may explain its antineoplastic effects.

Additional mechanisms for metformin's effects in cancer have been proposed and include:

- Inhibition of CSCs (as evidenced in Brown and colleagues 2020).
- Reversal of immune suppression through AMPK activation (Li et al 2018).
- Inhibition of epigenetic alterations associated with cancer progression (Tang et al 2018).

AMPK is central to the activation of these disparate pathways, highlighting the importance of studies that report increases in this compound (Godara et al 2020, Hadad et al 2015).

Future Directions for Research

As of March 2021, over 100 active clinical trials of metformin in cancer were registered at www.clinicaltrials.gov. Although the utility of metformin in a non-diabetic, cancer-affected population is still incompletely understood, there are enough signals of benefit in the current research to warrant further investigation. One of particular interest to this author is NCT01101438 (completion February 2022): "A Phase III Randomized Trial of Metformin vs Placebo in Early-Stage Breast Cancer". To date, over 3600 participants have been recruited to take metformin or placebo alongside standard of care for five years. This large trial is expected to make a significant contribution to our understanding of the therapeutic potential of metformin in cancer.

Future directions for research should seek to understand the apparent disparity between the encouraging results seen in case control and cohort studies and the inconsistent results in disease-based outcomes in controlled trials. Have observational studies severely overestimated the impact of metformin, or have we simply not identified the populations that may benefit from this

intervention? Optimal dose and treatment duration and ideal disease targets must also be established through prospective trials.

Future studies examining clinically relevant outcomes such as progression and mortality would ideally incorporate evaluations of markers of proliferation, immune activity, or biochemical changes. The inclusion of biometric data would help to illuminate the contribution of perceived improvements in risk factors (insulin resistance, BMI) to concrete outcomes like survival.

Finally, future research should also investigate the anti-neoplastic effects of metformin in its original target population, patients with Type II diabetes. While observational studies show significant promise, it is not yet clear whether metformin should be prioritized over other glucose-lowering agents for its potential effects in cancer.

CONCLUSION

Observational research has suggested that metformin may possess significant anti-neoplastic activity, but its action in non-diabetic patients remains uncertain. This study summarizes the available data from 23 clinical trials and one case report in non-diabetic individuals. While metformin appears to have measurable benefit in pre-cancerous conditions and may influence cancer risk factors, its effects in survival outcomes are less certain. Future investigation is required to identify the ideal parameters of metformin use in in non-diabetic individuals.

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