Nutritional Medicine Journal

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Nutritional Medicine Journal

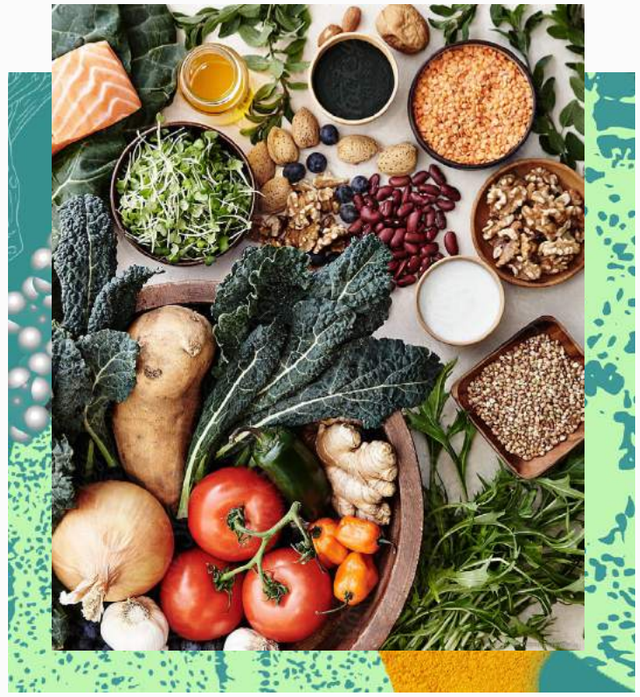
Curcumin: A Review of Clinical Use and Efficacy | Inflammatory Bowel Disease | Butyrate Therapy | Ashwagandha: A Review of Clinical Use and Efficacy | Magnesium: A Review of Clinical Use and Efficacy | Coenzyme Q10: A Review of Clinical Use and Efficacy

NUTRITIONAL MEDICINE JOURNAL

The Nutritional Medicine Journal (NMJ) is a specialist peer-reviewed scientific publication related to the application of personalised dietary interventions, foods, dietary factors, and nutritional supplements in clinical practice.

Topics include clinical nutrition, personalised nutrition, lifestyle medicine in the context of nutritional medicine, micronutrients, amino acids, fatty acids, phytochemicals, probiotics, prebiotics, and functional beverages and foods.

The aim of the NMJ is to provide health professionals with authoritative and scientifically accurate articles on topics in nutritional medicine.



Nutritional Medicine Journal

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Cover
Microscopic image of biopsy obtained during colonoscopy from a patient with painful bloody diarrhea showing chronic ulcerative colitis, a type of inflammatory bowel disease (IBD). Turmeric or curcumin longa powder. Coenzyme Q10 ubiquinone CoQ10 molecule 3D render chemical structure. Ashwagandha plant. Raw Magnesite rock. Butyrate acid flat structure.

Nutritional Medicine in Primary Healthcare

Benjamin I. Brown

Dietary interventions and nutrient-based supplements can prevent disease, reverse established illness and improve health while being very safe and, in some cases, extraordinarily effective. Yet the scientific evidence for nutritional medicine is not well incorporated into medical training, and consequently nutritional therapy is underutilised in clinical practice to the detriment of good patient care.

What we eat is a major modifiable determinant of health. Dietary risk factors have been attributed to 11 million deaths amongst adults aged 25 years or older worldwide, 18% of all deaths in North America, and 22% of all deaths in Europe.[1] Adoption of healthier eating predictably reduces the risk of death and major chronic diseases.[2] A large number of studies assessing the impact of dietary interventions on metabolic risk markers and hard endpoints have demonstrated important disease-modifying effects in areas such as cardiometabolic disease[3,4,5] autoimmune disorders[6,7] functional gastrointestinal disease,[8] endocrinological disease,[9] cancers[10,11,12] dermatological diseases[13,14] psychiatric illness[15,16,17] and neurodegenerative disease.[18,19,20]

The mechanisms by which food and food components such as micronutrients and other bioactive compounds prevent and treat disease include mitigation of DNA damage, maintenance of cell and tissue function, by acting as cofactors or components to thousands of metabolic processes, and involvement in biological processes intrinsic to health and longevity.[21,22]

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Despite the importance of an optimal daily supply of nutrients from food, most of the population have nutritional inadequacies. Amongst participants of the Heath Survey for England, 72% did not achieve the recommendations for daily fruit and vegetable intake.[23] Inadequate intake of micronutrients is a widespread public health problem globally.[24] In the UK, young adults are typically deficient in several essential micronutrients,[25] with the problem more pronounced in groups at higher risk of nutritional inadequacy, including children with poor-quality diets,[26] people consuming vegan diets,[27] pregnant women[28] and older adults.[29]

Even when consuming a relatively healthy diet, suboptimal micronutrient intakes can occur due to environmental factors related to the industrialisation of the food supply that have reduced nutrient levels in foods. For example, over the last 80 years there have been significant declines in the mineral content of fruit and vegetable crops in the UK, likely due to factors such as choice of cultivar or plant variety, a shift from organic practices to industrial practices, deleterious changes in soil ecosystems, and increases in atmospheric carbon dioxide.[30] Exacerbating the issue of suboptimal food quality, an individual's metabolic requirements for many different nutrients may be higher due to inherent genetic variations,[31] psychological and environmental stress,[32] functional health status,[33] medication use[34] and age-related malabsorption,[35] amongst other influences.

Nutrient-based supplements can optimise micronutrient intake and reduce the risk of nutritional deficiencies in the general population,[36] as well as in groups at particularly high risk of suboptimal nutrient status.[37,38] Intervention studies provide evidence for therapeutic applications of nutrient-based supplements in a wide range of areas, including mental health (e.g. magnesium,[39] ω-3 polyunsaturated fatty acids,[40] n-acetylcysteine[41]), cardiovascular disease (e.g. ubiquinone,[42] vitamin C,[43] carnitine[44]), type-2 diabetes (e.g. resveratrol,[45] lipoic acid,[46] zinc[47]) and dementia (e.g. B vitamins[48]), to cite just a few examples in which nutrient-based supplements have been shown to prevent and/or treat disease.

There is enough evidence to incorporate nutrition in medicine; however, its implementation is lacking, in part due to poor nutritional literacy resulting from inadequacies in training[49] and longstanding bias against nutritional interventions.[50] This is despite an increasing appreciation for the role of nutrition in primary healthcare amongst medical students and a desire for improved education.[51,52] Better knowledge could facilitate the adoption of nutritional medicine and encourage interdisciplinary collaboration with clinical nutritionists, ultimately helping to bridge shortfalls in the management of nutrition-related disease.

The aim of the *Nutritional Medicine Journal* is to provide health professionals with authoritative and scientifically accurate articles on topics in nutritional medicine, with emphasis placed on publications relevant to the clinical application of patient-centred, integrative, personalised nutritional approaches that are focused on improving underlying pathophysiology or function to promote positive health outcomes.

Welcome to the inaugural issue.

Benjamin I. Brown
Editor, *Nutritional Medicine Journal*

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Editorial
Nutritional Medicine in Primary Healthcare

Curcumin:
A Review of Clinical Use and Efficacy

Karin Elgar

Abstract

Turmeric has a long tradition of use in Ayurvedic medicine for a variety of indications, including digestive and liver support, in mood-related disorders and inflammatory conditions. Modern research has confirmed anti-inflammatory, antioxidant, anti-microbial and anti-tumour activities of compounds isolated from turmeric, including curcumin and other curcuminoids. Curcumin has poor bioavailability and various formulations have therefore been developed to overcome this issue. Clinical trials have shown benefits of curcuminoids in a wide range of conditions, including cardiometabolic, inflammatory and mood disorders. Turmeric extracts have been found to be safe in humans with only mild adverse events being observed in clinical trials, mostly gastrointestinal disturbances, but due to its physiological actions, some drug interactions are possible.

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Introduction

Turmeric (*Curcuma longa*) is a member of the ginger family and has a long tradition of use not only as a culinary spice, but also in Chinese and Ayurvedic medicine for a variety of clinical uses, including digestive and liver support, in mood-related disorders and inflammatory conditions.[1] Curcumin is a yellow polyphenolic compound that gives turmeric its characteristic colour and, alongside other curcumoids including bisdemethoxycurcumin and demethoxycurcumin, is also one of the main active components thought to mediate its medicinal properties, which include anti-inflammatory, antioxidant, anti-microbial and anti-tumour activities.[2]

The bioavailability of curcumin is limited due to poor absorption and rapid metabolism through the liver, and various techniques have therefore been employed to increase bioavailability through different delivery systems.[3] Despite this, turmeric extracts seem to have good clinical efficacy, even without such enhancements (unformulated products), and it has been postulated that this may be due to the fact that some of the metabolites of curcumin also possess beneficial biological activities, some of which appear to have stronger antioxidant effects than curcumin itself.[4]

Piperine, a compound from black pepper, has been shown to enhance bioavailability by 20 times, and is therefore commonly added to curcumin supplements.[5] Other methodologies that have been used to increase the bioavailability of curcumin include hydrophilic nanoparticles and solid lipid particles.[6] Being lipid soluble, the solubility and absorption of curcumin is enhanced by the presence of lipids, either through a lipid-containing formulation such as solid lipid particles, or by taking it with a meal.[6] This is also the way that turmeric has been consumed, either as part of a meal or, in Ayurvedic tradition, in a milky drink.

The issues of bioavailability and the large variety of formulations on the market that claim to have enhanced bioavailability make it difficult to compare the dosages used in studies and suggest dose recommendations for specific indications. Where dosages have been suggested, they generally refer to non-enhanced formulations.

General Functions

Inflammation/inflammatory markers

Inflammation is a main driver for chronic degenerative disease, including cardiovascular disease (CVD), cancer, neurodegenerative conditions like Alzheimer's disease (AD), metabolic disorders, such as diabetes and obesity, and autoimmune conditions. As such, safe and effective anti-inflammatory compounds play an important role in the prevention and management of these conditions, and curcumin has shown promising anti-inflammatory effects in animal studies.[7] Its anti-inflammatory properties appear to be due to a number of mechanisms, including effects on cellular signalling, and modulating expression and release of pro- and anti-inflammatory cytokines (messenger molecules of the immune system that regulate inflammation).[7] Nuclear factor kappa B (NF-κB) is a key upregulator of the expression of pro-inflammatory cytokines, including tumour necrosis factor-alpha (TNF-α), interleukin (IL)-1, IL-6 and IL-8, and curcumin has been shown to have an inhibitory effect on NF-κB.[8] Curcumin also appears to exert a positive effect on the microbiome, which may contribute to its anti-inflammatory potential.[9,10]

The effects of curcumin on a large range of conditions associated with inflammation have therefore been studied in many human clinical trials, and many of these studies have assessed inflammatory markers to elucidate specific mechanisms by which curcumin works.

Two recent meta-analyses looked at studies evaluating inflammatory markers and, although they included largely the same studies,

came to differing results. In one review, improvements in C-reactive protein (CRP), high-sensitivity CRP (hsCRP), IL-1 beta, IL-6 and TNF-α failed to reach statistical significance;[7] however, the other review found statistically significant improvements in IL-6 and hsCRP but not TNF-α.[11] These contradictory results may be due to the high heterogeneity of trial results observed in both meta-analyses.

Two meta-analyses looked at individual markers. One, which included nine randomised-controlled trials (RCTs) with 609 participants, found that curcumin significantly decreased IL-6.[12] A subgroup analysis suggested that taking curcumin for more than 8 weeks is more beneficial, whilst dosages lower than 1000 mg per day and unformulated supplements were more effective than higher dosages and formulated products. The reasons for these findings are unclear, and are not further discussed by the authors. The other review, which included eight RCTs and 549 participants, looked at TNF-α, and found a significant lowering of TNF-α in those taking curcumin compared with placebo.[13] There appeared to be no association with duration or dosage but, again, unformulated products appeared to be more effective. This may be due to compounds other than curcumin that have also been shown to have biological activities.[2]

Many more studies, not included in the above meta-analyses, have looked at inflammatory markers as part of the evaluation of curcumin for particular disorders. On the whole, those that included several markers found significant decreases in at least some of them in patients with a variety of underlying health conditions, including metabolic syndrome (metS),[14] non-alcoholic fatty liver disease (NAFLD),[15,16,17] kidney disease with haemodialysis,[18] ulcerative colitis,[19] obesity,[20,21] diabetes[22] and schizophrenia.[23] On the other hand, a number of studies that only included one or two markers found no benefits or the benefits failed to reach statistical significance versus placebo.[24,25,26,27]

Supplementation regimes varied widely in all of these studies in terms of formulations (including both turmeric and curcumin/curcuminoid supplements, with or without enhanced bioavailability), dosage (46–4000 mg curcumin) and duration (4–36 weeks), as well as in the study populations, for example, patients with inflammatory or metabolic disorders.

Although the evidence is mixed, overall it suggests that curcumin has anti-inflammatory effects in humans, which may depend on dose and duration of supplementation as well as study population. The clinical findings from a variety of inflammatory conditions (see 'Clinical uses') also support an anti-inflammatory effect.

Oxidative stress

Oxidative stress is characterised by an imbalance between the production and elimination of reactive oxygen species or 'free radicals'. Oxidative stress plays an important role in inflammation, and has been associated with aging and chronic disease. Malondialdehyde (MDA), an end-product of lipid peroxidation, and the two antioxidant enzymes glutathione peroxidase (GPX) and superoxide dismutase (SOD) are commonly used markers of oxidative stress, and numerous preclinical studies, including in vitro and animal studies, have shown that curcumin can increase these markers.[28]

Two recent meta-analyses looked at the effects of curcumin on oxidative stress markers in humans. Both found that curcumin significantly reduced MDA levels.[11,28] One found that curcumin also significantly increased SOD,[28] whilst in the other this failed to reach statistical significance versus placebo.[11] The former review also evaluated GPX and found no significant benefit, although this was based on only two studies.

Since then, some further studies have found contradictory results, with some showing significant benefits in some antioxidant markers,[29,30] and some showing no benefits,[24,26] using a variety of markers.

Dosages varied widely, from 46 to 1500 mg per day for 4–24 weeks. Dosages of above 800 mg per day and formulations including piperine were found to be more effective in lowering MDA than lower dosages and formulations without piperine.[28]

The reasons for the contradictory results are unclear, but may be due to the heterogeneity of the studies, with regards to dose, formulation, duration and study population. Where there is clear evidence in a particular indication, this will be discussed below in 'Clinical uses'.

Clinical Uses

Alzheimer's disease (AD) /cognitive function

The most common neurodegenerative disease is AD, affecting more than 35 million people worldwide, and is characterised by memory loss and cognitive impairment. The main histopathological feature of AD is amyloid-β plaques, and preclinical research suggests that curcumin can directly affect the processes involved.[31] A human study in non-demented adults has also shown that cognitive and behavioural benefits (from curcumin intervention) are associated with decreases in plaques and accumulation of tau tangles (clumps of the protein tau, which is essential for brain cells to work properly) in brain regions that regulate mood and behaviour, a hallmark of AD.[32]

A series of three cases with AD in 2012 reported benefits in cognitive function with curcumin (764 g turmeric providing 100 mg curcumin per day) after 12 months of supplementation.[33] All three patients took curcumin for at least 1 year, and did not experience any deterioration. However, two double-blind, placebo-controlled trials did not confirm such benefits of curcumin at doses of up to 4000 mg per day for 6 months on clinical parameters and/or biomarkers.[34,35]

Despite promising preclinical evidence on the effectiveness of curcumin in AD, so far clinical research has failed to demonstrate statistically significant effects.[31] It is important though to bear in mind that AD is a complex condition and, in view of the anti-inflammatory, antioxidant and possibly anti-amyloid properties of curcumin, one could consider including it in a more comprehensive programme, although at present there is no evidence for this from RCTs.

A study in people at high risk of developing type 2 diabetes mellitus (T2DM) found that curcumin reduced circulating levels of islet amyloid polypeptide and glycogen synthase kinase-3, compounds that may link T2DM and AD, suggesting that curcumin may help reduce the risk of developing AD as well as T2DM.[36]

A number of RCTs have also been carried out on cognitive function in healthy, middle-aged and elderly people, as well as in people with schizophrenia. Some studies have found curcumin to be significantly better than placebo in improving cognitive function (including memory) in middle-aged and elderly people without dementia,[32,37,38,39] whilst other studies found no significant benefit.[32,40,41] Dosages ranged from 80 to 1500 mg curcumin per day, and study durations ranged from 4 weeks to 18 months, with positive and nil studies amongst both shorter- and longer-term studies. Positive effects on cognitive function have even been seen with acute single-dose administration.[39] The somewhat contradictory results may be explained by the variety of formulations used that are likely to have different bioavailabilities.

One double-blind, placebo-controlled trial in people with schizophrenia found that 8 weeks of curcumin supplementation improved cognitive function.[23] Another 8-week RCT in schizophrenia found no significant improvements in cognitive function but noted an increase in brain-derived neurotrophic factor, which is generally lower in people with schizophrenia, in the curcumin but not in the placebo group.[42] Whilst limited, the results in schizophrenia are promising, and may suggest that a longer duration of curcumin administration may be needed to see benefits in cognitive function.

Arthritis

Osteoarthritis

Osteoarthritis is a common degenerative joint disease that is characterised by progressive loss of cartilage in the joints. This is thought to be due to 'wear and tear', but inflammatory processes have also been shown to be involved, and standard treatment is usually with non-steroidal anti-inflammatory drugs (NSAIDs).[43,44]

Due to its anti-inflammatory action, curcumin has become a popular natural alternative to NSAIDs, which can have significant side-effects, in particular in terms of the digestive system. There is an overwhelmingly positive body of clinical and preclinical research into the use of curcumin and curcuminoids in osteoarthritis.

Three recent meta-analyses[43,44,45] of 10 studies altogether have come to the conclusion that curcumin is significantly better than placebo and as effective as some NSAIDs in relieving pain and improving function and quality of life, and reducing the use of rescue medication such as paracetamol (acetaminophen). A variety of curcumin preparations have been used in the included studies at dosages of 180–2000 mg per day for 4–16 weeks.

Since then, in 2019 and 2020, several more RCTs have been published, all showing significant improvements in pain and other outcomes measured.[46,47,48,49,50,51] Many of the studies showed a halving in pain score with curcumin supplements,[49,50,51] and curcumin was not only found to be superior to placebo but also as effective as NSAIDs in relieving symptoms.[50,51]

Studies have lasted from 4 weeks to 6 months, and dosages have varied considerably, depending on the formulation used, with as low as 80 mg per day for reportedly highly bioavailable formulations to 1500 mg per day. One study evaluated short-term benefits (3 days and 1 week), and found that whilst both curcumin and placebo relieved symptoms to a similar extent in that short time-frame, the curcumin group saw a significantly greater reduction in hsCRP.[52] It would therefore be advisable to supplement for at least 4 weeks (3 months would be better) to see significant beneficial effects.

The anti-inflammatory and antioxidant properties of curcumin are thought to mediate its benefits in osteoarthritis, and a number of studies have found reductions in various markers of inflammation[48,52,53] and oxidative stress in patients with osteoarthritis.[54] Reductions in markers of cartilage matrix degradation have also been reported.[55]

Rheumatoid arthritis

RA is an autoimmune disease with inflammation of the joints, leading to their progressive destruction. As many of the conventional disease-modifying anti-rheumatic drugs can have severe side-effects, there has been increasing interest in natural anti-inflammatory treatments.

Four RCTs (three double-blind, one single-blind) have studied the potential benefits of curcumin in RA. Two of them showed statistically significantly better improvements than placebo in disease activity and clinical symptoms,[56,57] whilst one showed curcumin to be better than diclofenac (an NSAID) with fewer side-effects.[58] In all three studies, disease activity and/or symptoms scores approximately halved. The fourth study found significant improvements in disease activity and symptoms in both the curcumin and the placebo groups, and although the curcumin group improved more, this failed to reach statistical significance.[59]

Dosages ranged from 120 to 500 mg per day for 8 weeks to 3 months. The study with the non-significant results only used 120 mg per day,[59] and one study compared 250 mg with 500 mg and found both dosages to be equally efficacious.[57]

Overall, curcumin appears to be beneficial in RA at dosages of 250–500 mg for 3 months.

All four studies cited above also reported significant improvements in inflammatory markers, suggesting the anti-inflammatory properties of curcumin to be an important mechanism of action.

Asthma

Curcumin has been used for asthma in India and China for centuries, and preclinical research has confirmed its potential for alleviating asthma, through its anti-inflammatory action, in particular with respect to inflammation of the smooth muscles of the airways, which are affected in asthma.[60]

Two RCTs in adults found no clinical benefits, although one RCT using 1000 mg per day for 1 month[61] found significant improvements in FEV1 (a measure of airway obstruction), whereas the other study used 2000 mg per day for 6 months and found no such improvement.[60] The latter study was double-blind whilst the former was an open-label RCT, therefore a placebo effect may explain the difference. A more recent double-blind, placebo-controlled trial in 34 children and adolescents with asthma found that turmeric powder improved night-time awakening, use of rescue medication and overall disease control significantly more in the turmeric group compared with the placebo group.[62] Both groups saw significant improvements in frequency of symptoms and interference of activity, with no statistically significant difference between the groups.

Whilst turmeric powder appears to be promising for children and adolescents, there is no evidence for a benefit of curcumin in adults with asthma.

Cancer

According to the National Cancer Institute, almost 40% of people in the USA will be diagnosed with cancer at some point in their lives and about a third will die from the disease.[63] Cancer treatments are expensive and are often accompanied by serious side-effects. A plethora of preclinical research studies have shown benefits of curcumin in both cancer initiation and progression.[64]

A recent review of 22 human clinical studies[64] found benefits of curcumin, as an adjunct to standard treatment, in a variety of common cancers, such as breast, prostate, pancreatic and colorectal. These benefits, some of which have been confirmed by further studies, have included:

- Reduced side-effects of chemo- or radiotherapy;[65,66]
- Increased survival rate;
- Improved quality of life;
- Reductions in pre-cancerous lesions;
- Increased effectiveness of treatment;[65,67]
- Decrease in tumour markers.[66]

A meta-analysis looking at six trials of curcumin, four with topical and two with oral application, on treatment-induced oral mucositis (an inflammation of the lining of the mouth, a common side-effect of both chemo- and radiotherapy) in patients with head and neck cancers found curcumin to reduce the severity of oral mucositis and weight loss, which is often caused by the treatment (chemo- and/or radiotherapy).[68]

Formulations, and with that potential differences in bioavailability, dosages and duration of curcumin supplementation have varied significantly, with doses of up to 8 g per day for 11 months being reported to be safe and well tolerated.[69] Evaluated outcome measures, concomitant chemo-/radiotherapy regimes and study designs have also differed from trial to trial, making it difficult to suggest a particular dose for a particular cancer.

A number of mechanisms are thought to be involved in the anti-cancer effects of curcumin, including anti-angiogenic effects (interfering with the blood supply to the tumour), induction of apoptosis (programmed cell death), interfering with the cell proliferation cycle of tumour cells, and inhibition of the tumour's invasion of healthy tissues. There is also a strong relationship between inflammation and cancer, so the anti-inflammatory properties of curcumin are also thought to play a role in its anti-tumour effects.[64]

Cardiometabolic conditions and risk factors

Dyslipidaemia

Dyslipidaemia is characterised by increased triglycerides (TGs), total cholesterol (TC) and/or low-density lipoprotein (LDL) cholesterol, and/or decreased high-density lipoprotein (HDL) cholesterol, and is considered an important risk factor for CVD. It is commonly associated with overweight/obesity, metabolic disturbances such as T2DM and NAFLD.[70]

A 2019 review and meta-analysis of the effects of curcumin on blood lipids in patients with metabolic disorders found statistically and clinically significant beneficial effects on TGs, TC, LDL and HDL cholesterol, although there was considerable heterogeneity amongst the included studies.[70] Results were generally better with higher dosages, longer duration and in patients with T2DM.

These findings have been confirmed by further double-blind, placebo-controlled trials in a range of patient populations, including women with polycystic ovary syndrome (PCOS),[71] in overweight women together with exercise,[72] patients with NAFLD,[16,73,74] young obese men,[75] patients at high risk of T2DM,[76] patients with T2DM[22,26] and patients with elevated CVD risk,[21] although not necessarily all lipid parameters were significantly improved in all studies. In a few RCTs, however, lipid profiles were not significantly improved.[18,25,77,78]

Dosages reported were generally in the range of 40–1800 mg per day, the lower dosages often being nano-formulations, and the duration of supplementation was 4 weeks to 6 months. A common dose range that showed benefits was 1000–1500 mg per day for at least 8 weeks.

A number of mechanisms for the lipid-lowering potential of curcumin have been discussed, including its modulation of the expression of factors involved in regulating lipid metabolism, such as adiponectin, resistin and leptin.[22,70,79,80]

Endothelial dysfunction

The endothelium is the inner layer of blood vessels, and it controls vascular relaxation and contraction. In endothelial dysfunction (ED), there is an imbalance between vasodilating substances (that widen the blood vessels) and vasoconstricting substances (that narrow the blood vessels). ED is involved in the development of atherosclerosis and, as such, is a risk factor for CVD. High blood pressure, smoking and diabetes are thought to contribute to ED.[81] The most commonly used method to evaluate ED is a flow-mediated dilation (FMD) test.[82]

A couple of recent meta-analyses, 1 of 5 and 1 of 10 studies, found that curcumin is effective in improving FMD, although improvements in other ED measurements failed to reach statistical significance.[83,84] Since publication of the above reviews, a further long-term[85] and an acute curcumin supplementation trial[86] have reported beneficial effects, whilst another long-term trial reported no improvement in ED.[75]

Depending on formulation, dosages ranged from 25 mg to 2000 mg per day, for 4–24 weeks. Neither dose nor duration appeared to explain the heterogeneity of the results.

Although not all trials report benefits, the overall evidence suggests that curcumin can help improve endothelial function. Turmeric at a dose of 1200 mg per day for 12 weeks has shown benefits.[85]

It is thought that the benefits of curcumin for endothelial function are due to its anti-inflammatory and antioxidant properties,[84] a lower dose may suffice with a more concentrated or bioavailable formulation.

Hypertension

Hypertension is the largest known risk factor for heart disease and, globally, hypertension is the second biggest risk factor for overall mortality and morbidity after poor diet.[87] In 2015, one in four men and one in five women worldwide had high blood pressure.[86,87,88]

A 2019 meta-analysis of 11 RCTs on the effects of curcumin on blood pressure found a significant benefit for lowering systolic but not diastolic blood pressure, but only in studies with a duration of 12 weeks or longer.[89] Subgroup analysis did not show any effect of the participants' condition or the type of formulation of curcumin used. Results from some more recent RCTs are also mixed.[73,90]

Although the evidence for the use of curcumin in hypertension is weak, the fact that hypertension is commonly associated with other cardiovascular or metabolic risk factors for which curcumin has been shown to be beneficial suggests that curcumin may still be worth considering for patients with hypertension.

Metabolic syndrome

MetS is not a disease as such but a cluster of cardiovascular risk factors, and is defined as a combination of at least three of the following metabolic abnormalities: elevated TGs, decreased HDL cholesterol, hypertension, elevated blood sugar, and central obesity [increased waist circumference (WC)].[91] The risk of developing metS increases with age, and it is estimated to affect 40% of those over 50 years old in the USA and nearly 30% in Europe, and insulin resistance is thought to play an important part in the development of metS.[92]

A meta-analysis of 7 RCTs including 503 participants with metS found that curcumin supplementation led to significant improvements in fasting blood glucose, TGs, HDL cholesterol and diastolic blood pressure, but failed to reach statistical significance for WC and systolic blood pressure.[93] The findings regarding the effect on hypertension are contradictory to the findings in another meta-analysis, discussed in the 'Hypertension' section, which found a significant decrease with systolic but not diastolic blood pressure.[89] The reasons for these contradictory results are not clear, but may be due to different study populations. Dosages used ranged from 800 to 2400 mg per day for 4–12 weeks.

Another meta-analysis looked more specifically at obesity-related parameters in patients with either metS or related metabolic disorders, including T2DM and NAFLD.[94] The pooled data showed that curcumin had benefits in terms of reduced body mass index (BMI), weight and WC, as well as improved leptin and adiponectin levels, two important metabolic messenger molecules.

Curcumin has also been shown to decrease markers of inflammation and oxidative stress in patients with metS,[14] although another study showed no benefits of curcumin on pro-oxidant antioxidant balance.[30]

Overall, curcumin appears to be beneficial for people with metS, and could be suggested at a dose of at least 800 mg for at least 8 weeks.

Possible mechanisms for the benefits of curcumin in metS include reduced oxidative stress and modulation of genes involved in glucose and lipid metabolism.[93]

Type 2 diabetes mellitus

T2DM is caused by impaired insulin secretion and insulin resistance, and is an important risk factor for CVD. T2DM, especially when poorly controlled, can also lead to a number of complications, such as diabetic nephropathy, retinopathy and neuropathy.[95]

There has been a significant increase in T2DM over the past decades, and it was estimated that in 2018/2019, 4.8 million people in the UK had diabetes, with about a fifth not being aware that they had the disease, and a further 13.6 million at risk of developing T2DM.[96] As such, T2DM poses an enormous public health risk and burden.

Improving glycaemic (blood sugar) control is key in the management of T2DM and reducing the associated longer-term risks. A 2018 meta-analysis, including 11 studies and 1144 participants, looked at the effects of curcumin on glycaemic control in both diabetic and non-diabetic patients and found that, in people with diabetes and prediabetes, curcumin had a positive

effect on fasting blood sugar and HbA1c (a marker of blood glucose levels over the past 2–3 months), but not HOMA-IR (a method used to estimate insulin resistance and function of the beta-cells that secrete insulin).[97] Improvements in glycaemic control have also been seen in women with PCOS.[71] Formulations varied widely in the studies, and effects were seen with curcumin and curcuminoids but not turmeric; curcumin dosages ranged from 70 to 4000 mg per day, and durations from 4 to 36 weeks.

People with diabetes also commonly have other cardiovascular risk factors, and studies have shown that curcumin can improve lipid profiles,[22,26,90,98,99] endothelial function,[85] inflammatory markers[22] and obesity[26,27,90,100] in diabetics.

A number of small pilot studies have also found beneficial effects on a number of diabetic complications, including diabetic sensorimotor polyneuropathy,[101] eye conditions,[102,103] kidney disease[104,105] and microangiopathy (a disease of the small blood vessels that leads to other complications).[102,106]

Curcumin has also been shown to be beneficial in the prevention of T2DM. A double-blind, placebo-controlled study of 240 people with prediabetes found that none of the patients on curcumin progressed to T2DM over the study duration of 9 months, whilst 16.4% of the placebo group did.[107] Indicators of glycaemic control and beta-cell function were also significantly better in the curcumin group at the end of the study. The dosage of curcumin in this study was 1500 mg per day for 9 months.

Based on the available data, the benefits of supplementation with curcumin for patients with diabetes or prediabetes are well demonstrated. Dosages varied widely in the clinical trials, and may depend on the specific formulation. Using a dosage of at least 500 mg per day for at least 8 weeks could be suggested, with a lower dose for formulations with particularly high bioavailability.

A number of possible mechanisms have been suggested, including the antioxidant and anti-inflammatory properties of curcumin, and its ability to modulate the functions of various cell signalling molecules.[97] Curcumin can modulate the gut microbiota in diabetics and with that the concentration of lipo-polysaccharides in the blood, which may contribute to the anti-inflammatory action of curcumin.[104] Curcumin has also been shown to reduce free fatty acids, which are thought to mediate insulin resistance.[108]

Digestive conditions

Gallbladder function

Turmeric is considered a cholagogue, a substance triggering contraction of the gallbladder to promote bile flow, and is commonly used as such in naturopathic tradition to support fat digestion and detoxification.

Two early ultrasound studies indeed showed that curcumin led to gallbladder contraction, with 40 mg triggering a 51% decrease in gallbladder volume and 80 mg a reduction of 72%.[109,110] A more recent study in healthy volunteers also showed beneficial effects of a turmeric-based drink on bile acid metabolism when taken before a medium- or high-fat breakfast.[111]

Clinical research into gallbladder disease is scarce. One small, open-label pilot study in patients with primary sclerosing cholangitis, a chronic disease in which the bile ducts inside and outside the liver become inflamed and scarred, potentially leading to narrowing and blockage, found no benefit of curcumin (1500 mg per day for 12 weeks).[112]

Whilst curcumin has been shown to stimulate bile flow, research of its benefits in gallbladder disease is lacking.

Gastric ulcer/*Helicobacter pylori*

Turmeric has a long tradition of use for gastric ulcers and gastritis, in particular in Thailand.[113]

Some early studies from Thailand investigated the use of turmeric in gastric or duodenal ulcers. An open-label pilot study involving 25 patients with endoscopically confirmed ulcers found a significant benefit of 3000 mg of turmeric powder per day, with 48% of ulcers healed after 4 weeks and 76% after 12 weeks.[114] A double-blind, placebo-controlled study of 118 patients with duodenal ulcers, on the other hand, found no benefits of 6000 mg of turmeric for 8 weeks.[115] A double-blind study from 1989 found turmeric to be more beneficial than placebo in patients with dyspepsia syndrome, which may not be ulcer-related, with 87% and 53% of patients, respectively, reporting improvements.[113]

More recently, curcumin has been investigated for gastritis, gastric or duodenal ulcers associated with *Helicobacter pylori (H. pylori).* An open-label study found that 7 days of a combination of 60 mg of curcumin with lactoferrin, N-acetylcysteine and a proton pump inhibitor (PPI) led to a significant improvement in dyspeptic symptoms despite not eradicating *H. pylori.*[116] Whilst turmeric on its own has been shown to be ineffective in eradicating *H. pylori* or decreasing inflammatory markers in patients with chronic gastritis,[117] 2 RCTs showed that used alongside standard triple therapy (two antibiotics plus a PPI), curcumin led to a statistically significant improvement of the efficacy of treatment.[118,119]

Based on the results of the above studies, curcumin at a dose of 500 mg per day for 4 weeks would be a worthwhile add-on to triple therapy in *H. pylori*-related gastritis or ulcers, and turmeric may be beneficial for dyspeptic symptoms where no further diagnosis has been made.

Curcumin is well known for its anti-inflammatory properties. In this context it is thought that IL-8, an inflammatory cytokine that is involved in *H. pylori*-related inflammation, can be suppressed by curcumin.[119] The study by Judaki *et al.* also showed that curcumin decreased oxidative stress and oxidative DNA damage in the gastric mucosa.[120]

Inflammatory bowel disease

Inflammatory bowel disease (IBD) is characterised by chronic inflammation of the digestive tract. It includes ulcerative colitis, which affects the colon and rectum only, and Crohn's disease, which can affect any part of the digestive tract, from mouth to anus.

Several meta-analyses over the past few years have evaluated the same six original studies on ulcerative colitis, and found curcumin to be beneficial in inducing clinical and endoscopic remission and response.[121,122,123] Depending on statistical methodology and studies included, curcumin was found to be two to more than five times more effective than placebo. In one meta-analysis that included only three of the original studies in their meta-analysis, a different methodology was used and benefits failed to reach statistical significance.[124]

As with studies in other conditions, formulations and dosages varied widely. Whilst evidence as to the best dosage and duration is lacking, higher dosages (e.g. 3000 mg per day) or products with higher bioavailability and longer duration of supplementation (at least 3 months) appear to be of more benefit.[122]

There are fewer studies in patients with Crohn's disease. An early pilot study[125] involving 5 patients with Crohn's disease taking 1080 mg of curcumin for 1 month and then 1440 mg for another 2 months saw improvements in 4 patients, with an average decrease of disease activity of 20.8%. The fifth patient did not complete the study due to worsening of symptoms. 2 more studies were published in 2020. One double-blind, placebo-controlled trial in patients with mild to moderate disease found clinical remission rates of 35%, 40% and 40% at weeks 4, 8 and 12, respectively, which were significantly higher than those in the placebo group, and 15% endoscopic remission in the curcumin group versus 0% in the placebo group.[126] This study used 360 mg of Theracurmin per day. The second double-blind, placebo-controlled trial evaluated the effects of 3000 mg of curcumin per day for 6 months in 62 consecutive

patients with Crohn's disease undergoing bowel resection, and found no benefits of curcumin on post-operative recurrence; in fact, in patients on curcumin who had a recurrence it tended to be more severe, although this was not statistically significantly different from placebo.[127]

Curcumin has also been studied in paediatric IBD. In an open-label, dose-escalation study involving 9 children, aged 11–19 years, over 9 weeks with a maximum dose of 4000 mg per day, none of the children had a worsening of symptoms, whilst 2 with ulcerative colitis and one with Crohn's disease saw improvements.[128]

Whilst the evidence is strongly in favour of the use of curcumin for ulcerative colitis, whether there are benefits in Crohn's disease is unclear. A suggested dose for ulcerative colitis would be 3000 mg per day for at least 3 months.

The anti-inflammatory actions of curcumin, including its effects on IL-1, TNF-α and other cytokines, are thought to mediate its benefits in IBD.[121]

Irritable bowel syndrome

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder, characterised by symptoms such as abdominal pain, altered bowel habits and changes in stool frequency, which can significantly impact on quality of life. The causes are unclear and are likely to be multi-factorial, with disturbances in the microbiome often playing an important role.[129]

Only 2 studies looked at curcumin on its own in patients with IBS. A double-blind, placebo-controlled study reported no benefits,[130] whilst an open-label, uncontrolled trial reported significant benefits.[129] In neither of these studies was the actual dose of curcumin clearly reported.

A review lists 3 clinical trials that used curcumin in combination with other herbs and/or nutrients, and reports positive results in 2 of the studies.[131] A combination with fennel essential oil appears to be particularly beneficial, with improvements in the severity and symptoms of IBS, as well as quality of life.[120,132]

At this point, there is insufficient evidence to suggest that curcumin on its own is effective in relieving IBS symptoms.

Exercise recovery/performance

Due to its anti-inflammatory and antioxidant effects, curcumin has received considerable attention for its potential benefits in sports nutrition.

2 recent reviews of 11 studies[10,133] and 1 meta-analysis[134] of 9 RCTs found significant effects of curcumin in reducing muscle soreness and creatine kinase (a marker of muscle damage). 2 studies published in 2020 further corrobarated these conclusions.[135,136] Subgroup analysis of the meta-analysis suggested that statistically significant effects were seen at follow-up durations of more than 1 day and with higher dosages. It also suggested that untrained individuals benefit more than trained ones.

Beneficial effects have also been observed in terms of reduced inflammation and oxidative stress, superior recovery and muscle performance, better psychological and physiological responses (thermal and cardiovascular) during training, and improved gastrointestinal function.[10]

Dosages used in trials have varied widely, from 90 to 6000 mg per day. Most studies looked at the effects of acute, short-term supplementation (1–7 days), whilst some looked at longer durations (up to 3 months). Both short- and longer-term studies reported benefits. Longer-term studies have used 600–1500 mg per day for 4–8 weeks.

The known anti-inflammatory and antioxidant effects of curcumin are thought to confer the observed benefits at least in part. The negative effect of prolonged exercise on gastrointestinal function and the immune system may be ameliorated by curcumin through its positive effects on the microbiome, which plays an important role in modulating inflammation.[10]

Non-alcoholic fatty liver disease

NAFLD is a common disorder caused by a build-up of fat within liver cells. Risk factors include obesity/overweight, metS and T2DM.[137]

5 recent meta-analyses looked into the effects of curcumin on NAFLD, looking at different parameters. 2 found that curcumin significantly reduced liver enzymes,[138,139] 1 saw improvements in glucose and lipid metabolism,[140] and 1 found that curcumin reduced BMI and WC,[141] whilst another did not find benefits for weight/body composition.[142]

Since then, more RCTs have been published, with some not showing any benefits in decreasing liver enzymes,[143,144,145] whilst others found benefits in a number of biochemical markers,[73] inflammatory markers[15] and NAFLD severity (as per ultrasound).[15,144] The reasons for these discrepancies are unclear.

Overall, curcumin, but not turmeric, appears to offer benefits to patients with NAFLD, although studies sometimes arrive at contradictory results and conclusions. This may be due to the fact that the studies have used a wide range of formulations, dosages and durations, making it difficult to establish general recommendations. Higher dosages (at least 1000 mg per day) for at least 8 weeks may offer the best benefits.

Overweight/obesity

Overweight and obesity are closely associated with inflammation and metabolic abnormalities, and body weight, BMI and/or WC have been measured and reported in a number of studies looking at curcumin and cardiometabolic risk factors and conditions, such as metS and NAFLD.

Two recent meta-analyses pooled data from such studies, and found a significant effect of curcumin on decreasing weight, BMI and WC.[94,146] Dosages have varied from 200 to 2800 mg per day, and durations from 4 to 36 weeks, with generally better results with dosages of 1000 mg or over and duration of 8 weeks or longer.[146]

A number of additional RCTs since the publication of the reviews have come up with contradictory results, with some showing a benefit in terms of obesity,[72] and others not.[73,90,147] The reasons for the differing results are not clear and do not appear to be due to dosage or duration, but may be due to different patient groups, in that patients were considered healthy in the study that showed benefits, whilst patients in the other studies had metS,[147] T2DM[90] and suboptimal blood glucose, respectively.[73]

1 RCT evaluated curcumin, 500 mg per day for 10 weeks, alongside a diet, in obese adolescent girls and found no significant benefits over placebo on BMI, WC and hip circumference.[77]

Overall, the evidence suggests that curcumin is beneficial for weight loss in overweight or obese individuals, at doses of at least 1000 mg and for at least 8 weeks.

Psychiatric disorders

Depression/anxiety

In Ayurvedic medicine, curcumin has been used for centuries for depression and anxiety.[148] Inflammation can play an important role in depression[149] and, as such, curcumin has been investigated in depressive disorders.

2 meta-analyses, including 7 clinical trials on people with major depressive disorder, found significant effects of curcumin, alongside treatment with conventional anti-depressants, in improving both depression and anxiety.[150,151] A number of trials have also investigated the effects of curcumin on mood and anxiety in patients with other disorders and healthy elderly people with mixed results. Some studies showed significant improvements in mood and/or anxiety over placebo,[39,152,153] whilst a study combining curcumin with vitamin E found no benefit in reducing anxiety but significantly reduced hot flushes in post-menopausal women.[154]

Dosages ranged from 150 to 1500 mg per day and duration of trials was 4–12 weeks, with neither dose nor duration appearing to affect outcomes.[150]

Overall, there is good evidence for the use of curcumin in people with depression alongside anti-depressant medication, whilst the effects on mood and anxiety in people without diagnosed depression are less clear. Most studies showing beneficial effects were at a dose of 1000 mg per day for at least 6 weeks.

A number of mechanisms appear to be involved in the benefits of curcumin, including modulation of neurotransmitter concentrations, inflammation, excitotoxicity, neuroplasticity, hypothalamic–pituitary–adrenal imbalances, insulin resistance, oxidative stress and the endocannabinoid system.[148]

Schizophrenia

3 double-blind, placebo-controlled clinical trials have looked at curcumin as an add-on to the usual treatment in patients with schizophrenia. The one with the highest dose (3000 mg curcumin) and longest duration (24 weeks) saw significant improvements in some but not all schizophrenia assessment scores.[155] The other 2, using 360 mg and 180 mg, respectively, for 8 weeks, did not see any improvement in schizophrenia symptom scores; however, one saw an increase in levels of brain-derived neurotrophic factor,[42] whilst the other saw improvements in memory and reduced levels of the pro-inflammatory marker IL-6.[23]

Whilst evidence is scarce, in view of the excellent safety profile of curcumin, supplementation with curcumin, at 3000 mg for at least 24 weeks, could be suggested to patients with schizophrenia.

The antioxidant, anti-inflammatory and neuroprotective actions of curcumin are thought to mediate the observed benefits,[155] which the latter two studies appear to confirm.

Skin conditions

Oral lichen planus

OLP is an autoimmune disease affecting the mucous membranes of the mouth, leading to lesions and open sores. Conventional treatment is usually with topical or systemic corticosteroids, which carry the risk of potentially serious side-effects, especially with long-term use. Natural anti-inflammatory compounds, like curcumin, are therefore of interest.

4 RCTs have been published on the use of oral curcumin and OLP. 2 of them used 2000 mg per day for 4 and 7 weeks, respectively, and found no benefit.[156,157] A study using a much higher dose, 6000 mg per day, found significant improvements over placebo within the study period of 2 weeks.[158] A recent study compared nano-curcumin, 80 mg per day, with standard treatment with prednisone, 10 mg per day, for 1 month in a double-blind fashion and found the nano-curcumin to be as effective as prednisone, with both treatments resulting in significant improvements of symptoms.[159]

Although evidence is limited, curcumin seems to be promising for people with OLP, although it seems that high dosages or highly bioavailable formulations, rather than longer-term treatment, are required to see benefits.

The observed benefits are thought to be due to the anti-inflammatory potential of curcumin, although changes of CRP and IL-6 were measured in one trial and failed to reach statistically significant results.[158]

Psoriasis

Psoriasis is another autoimmune skin disorder, and is characterised by an increased production of skin cells, leading to red, flaky, crusty patches of skin that can be itchy or sore.

A number of RCTs have evaluated the efficacy of curcumin in psoriasis, and found that curcumin is beneficial in relieving symptoms on its own[160] as well as in combination with topical steroids,[161] acitretin (a vitamin A analogue commonly used to treat psoriasis)[162] and light therapy.[163,164] Formulations have varied widely, from curcumin nano-particles to a turmeric tonic, as have dosages, and trials lasted for 9–12 weeks.

Overall, curcumin is a promising natural compound to either use alone or alongside other treatments. A dose of 400 mg per day has been used successfully.[161]

The observed benefits are thought to be due to the anti-inflammatory, anti-angiogenic, antioxidant and anti-proliferative effects of curcumin, and a reduction in the pro-inflammatory marker IL-22, which is involved in the development of psoriasis, has been observed.[161]

Safety

In 2018, a review of preclinical as well as human clinical trials concluded that standardised powders and extracts of turmeric and curcumin were safe and non-toxic in humans.[165] This review suggested that formulations with higher bioavailability or nano-formulations may also be safe, although there were few studies on such supplements. The most commonly reported side-effects are gastrointestinal disturbances, including constipation, diarrhoea, flatulence, nausea and vomiting.[166,167] An overview of systematic reviews concluded that adverse events reported in clinical trials were generally mild and similar to placebo, and also lists the most common adverse events as abdominal pain, nausea and dyspepsia.[168]

However, there have been some concerns over hepatotoxic effects (toxic effects on the liver). A review of the Italian Phytovigilance system showed that between April 2002 and July 2019, 76 reports of suspected adverse reactions to turmeric-containing products were received, of which 39 referred to possible liver damage.[169] These included a cluster of 28 cases of hepatotoxicity, which were reported from the Tuscany region of Italy within 6 months in 2018/2019. A recent article evaluated 7 cases of hepatotoxicity suspected to be due to turmeric or curcumin supplementation, the dosages used in all cases were well within the range used in clinical trials.[166] These cases appear to be limited to a specific period and region, and the wider relevance of this is as yet unclear, bearing in mind that The European Food Safety Agency, the US Food and Drug Administration and the European Medicines Agency all have considered turmeric extracts with high curcumin concentrations as safe.[170]

Another potential safety issue of turmeric or its extracts is contamination with toxic substances, including lead[171,172] and metanil yellow (an illegal food dye),[172] therefore choosing a product from a reputable company is important.

Drug interactions

A number of potential drug interactions are listed on the Natural Medicines Database.[167] It should be noted that many of them are based on in vitro or animal experiments or theoretical considerations.

Due to its own therapeutic potential, curcumin may have an accumulative effect with certain medications, and should therefore be used with caution alongside:

- Anti-diabetic drugs;
- Blood-thinning drugs.

Due to its antioxidant effects, curcumin may interact with certain chemotherapy drugs:

- Alkylating agents;
- Anti-tumour antibiotics;
- Topoisomerase I inhibitors.

Curcumin may increase levels of the following drugs:

- Amlodipine;
- Docetaxel;
- Norfloxacin;
- P-glycoprotein substrates;
- Paclitaxel;
- Sulfasalazine;
- Tacrolimus.

Curcumin may reduce levels of the following drug:

- Talinolol.

Curcumin may interfere with certain Cytochrome P450 pathways, and may therefore affect the efficacy and safety of drugs that are metabolised through the same Cytochrome P450 enzymes.[165]

Due to the possible hepatotoxicity of curcumin, care should be taken alongside hepatotoxic drugs.[169]

Pregnancy and breastfeeding

In amounts commonly found in foods, turmeric and curcumin are considered to be 'likely safe' during pregnancy and breastfeeding.[173]

However, there are no data from human clinical trials on the use of turmeric extracts as dietary supplements during pregnancy. Whilst in vitro and animal research suggests that the anti-inflammatory effects of curcumin may be of benefit for a number of pregnancy-related complications, curcumin has also shown harmful effects in oocyte maturation, fertilisation and development of the blastocyst in animal studies.[174]

Not enough is known about using turmeric or curcumin as a dietary supplement during breastfeeding, and should therefore not be recommended.[173]

One double-blind, placebo-controlled study compared a herbal supplement containing fenugreek, ginger and turmeric with placebo for 4 weeks in breastfeeding mothers, and found that the herbal supplement led to an increase in milk production that was significantly greater than in the placebo group.[175] No differences in milk nutrient content or adverse effects in the infants were observed. Adverse events in the mothers, including excessive gas, were no more frequent than in the placebo group. The daily dose of turmeric in the supplement was 900 mg.

Children and adolescents

A number of clinical studies have been conducted in children and adolescents.

1 RCT in asthmatic children and adolescents, aged 7–18 years, saw no adverse reactions with powdered turmeric root, 30 mg per kg body weight (mg kg^{-1}) per day for 6 months, and found benefits in some symptoms.[62] An RCT in obese pubescent girls, taking 500 mg of curcumin daily for 10 weeks, reported mild headaches and nausea, which resolved through continual use of curcumin capsules.[29,77]

A dose-escalation study in children and adolescents, aged 11–18 years, with IBD went up to a maximum dose of 4000 mg of curcumin per day for 3 weeks with no serious reactions.[128] 2 patients experienced increased gassiness during 3 visits. Inconsistent reports of symptoms that occurred only once or resolved on their own were reported in the majority of patients but were not considered to be related to curcumin; they were mild and did not require a lowering of the dose. Laboratory values remained within normal range for the duration of the study.

Although clinical research using curcumin in children and adolescents is limited, the available evidence suggests that curcumin is safe at a daily dose of 30 mg kg^{-1} turmeric powder for up to 6 months in children from 7 years old, or 500 mg of curcumin per day for 10 weeks in adolescents.

Conclusion

The research reviewed in this paper suggests that curcumin is safe and effective in a range of disorders, in particular conditions associated with inflammation and/or increased oxidative stress. Various formulations and a large range of dosages have shown benefits in clinical trials, making it difficult to make specific recommendations. Concerns have been raised over possible hepatotoxic effects, although the relevance of such reports is unclear, and agencies in both the US and Europe consider turmeric extracts to be safe.

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Inflammatory Bowel Disease: Towards a Model for Personalised Nutritional Therapy

Benjamin I. Brown

Abstract

Inflammatory bowel disease (IBD) has a complex multifactorial aetiology involving interactions between environmental factors (including diet), the microbiome, genetics and the immune system, leading to dysfunctional immune responses and chronic inflammation. Dietary factors and gut dysbiosis have emerged as important treatment targets in the management of IBD as they are involved in the initiation and perpetuation of inflammation, and subsequently disease development and progression. Specific dietary approaches and nutritional interventions have some, albeit limited, clinical evidence to suggest they can modify gene expression, have anti-inflammatory effects, induce mucosal healing, normalise intestinal microbiota, reduce disease activity and/or help maintain remission. This review uses evidence from nutritional science to propose a theoretical pragmatic model for the personalisation of nutritional therapy in patients with active or latent IBD, incorporating disease-modifying dietary recommendations and nutrient-based supplements, primarily as adjuvant therapies, with the intention to stimulate further investigation and research.

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Introduction

Inflammatory bowel disease (IBD) refers to a group of chronic inflammatory autoimmune diseases, of which the most prevalent types are ulcerative colitis (UC) and Crohn's disease (CD), that have a frequency of > 0.3% of the population in industrialised countries.[1] UC primarily affects the colonic mucosa in a diffuse, continuous and superficial pattern.[2] In contrast, CD can affect any section of the gastrointestinal tract, including the small and/or large intestine, the mouth, oesophagus, stomach and anus.[3] Clinical symptoms of IBD include diarrhoea and/or constipation, passage of blood and/or mucus, abdominal pain and cramping, fever and signs of bowel obstruction, as well as diverse extraintestinal manifestations.[4]

The development of IBD involves an interaction between genetic influences, environmental factors, dysregulated immune responses and alterations of the gut microbiome.[5] Importantly, genetic factors only account for a small part of disease variance, emphasising the role of gut microbial factors, alterations in intestinal immune homeostasis and environmental influences in inducing gut inflammation.[6] Genetic backgrounds, life-long environmental exposures, microbial organisation and immune responses differ from person to person, and give rise to remarkably complex disease processes that are highly variable, suggesting that there are multiple disease subtypes or that each individual has a pathophysiology that is unique.[7] This biological heterogeneity and complexity may help explain why traditional therapeutic interventions that target chronic inflammation have limited effectiveness and ultimately fail.[8]

Drug therapy of IBD centres on induction and maintenance of remission. Common drug treatments include aminosalicylates, corticosteroids, thiopurines, methotrexate and anti-tumour necrosis factor (TNF) agents.[9] While drug therapy can help reduce symptoms and induce remission, 90% of people with UC and CD may experience a relapsing course of their illness.[10,11] Limitations of efficacy and toxicity of traditional drug treatments might be overcome with the development of personalised therapies based on advances in understanding of disease pathophysiology.[12]

A better model for the management of IBD could consider the multiple antecedents, triggers and mediators that interact to produce gut immune dysregulation and uncontrolled inflammation as opportunities for personalised interventions that target an individual's underlying pathophysiology.[13] This approach has been termed 'functional medicine', and developed as a clinical operating model that enables healthcare providers to leverage evidence-based integrative therapies in a highly personalised way.[14,15] Considerable research has provided evidence for modifiable environmental and lifestyle factors,[16] microbiota-targeted therapies,[17] dietary interventions,[18] and herbal and nutritional medicines[19] that could be individually tailored to improve acute treatment and maintenance of remission in patients with IBD.

The aim of this narrative review is to explore clinical evidence for nutritional interventions that may influence the disease course and thus be candidates for the treatment of active disease and maintenance of remission. Nutritional interventions are then organised into a pragmatic integrative model for personalised patient management that could be explored in further clinical research.

Dietary interventions

There are number of dietary risk factors for the development of IBD, many of which are typical of industrialised dietary patterns; high intakes of red meat, refined sugar, total fat and omega-6 fatty acids, and low intakes of dietary fibre, fruit and vegetables.[20] Diet is a potent modifier of gene expression, gut microbial composition and mucosal immunity, all of which play a fundamental part in both risk and the progression of IBD.[21] Observations from epidemiological and experimental studies have resulted in the formulation and evaluation of dietary interventions designed to halt disease

progression and maintain remission in patients with IBD with clinical evidence that dietary therapy plays an important role in disease treatment (summarised in Table 3).[22,23,24]

Healthy diets

A traditional Mediterranean-style diet (MED-DIET) modified to reduce inflammation and exclude foods that aggravate CD was found to result in a trend towards reduction in biomarkers of inflammation [C-reactive protein (CRP) and micronuclei numbers], a change in the expression of inflammation-relevant genes, and improvement in gut bacterial diversity after 6 weeks.[25] In this study, patients were provided with food items including salmon, organic avocados, sweet potato, a variety of vegetables, gluten-free bread, extra virgin olive oil, green tea, honey, and fish oil capsules. Another study assessed the multidimensional impact of a MED-DIET in patients with IBD over 6 months, and found the diet significantly reduced malnutrition-related parameters (improved body composition), liver steatosis, disease activity, and the inflammatory biomarkers CRP and faecal calprotectin.[26] Similarly, a MED-DIET improved nutritional status and reduced faecal calprotectin in paediatric patients with IBD.[27]

A low-fat, high-fibre diet (10% of calories from fat) was compared with an improved standard American diet (35–40% of calories from fat, with increased fruit and vegetable intake) in a parallel-group, crossover study of 17 patients with UC in remission or with mild disease over 4-week dietary intervention periods. Primary outcomes were quality of life, markers of inflammation, and faecal markers of intestinal dysbiosis. Although both diets improved quality of life, the low-fat, high-fibre diet decreased markers of inflammation and reduced several biomarkers of intestinal dysbiosis.[28]

A semi-vegetarian high-fibre Japanese diet that includes a gradual transition from white to brown rice, eggs, milk, miso soup, vegetables, fruits, legumes, potatoes, pickled vegetables and plain yoghurt daily, with fish once a week and meat once every 2 weeks, was found to be effective at maintaining remission in adults with CD in a 2-year prospective study. Remission was maintained at 94% in the semi-vegetarian diet group versus 33% in controls, and relapse rates at 1 year and 2 years were 0% and 8% versus 33% and 75% in controls. Furthermore, the semi-vegetarian diet was associated with normal CRP in more than half of the patients.[29]

Several additional reports have subsequently supported the efficacy of the semi-vegetarian diet. In a case report, the semi-vegetarian diet was found to induce remission without medication in a patient with UC that developed after a low-carbohydrate weight-loss diet.[30] In another case report, the semi-vegetarian diet was used to successfully treat recent onset of UC during pregnancy.[31] A study examining the effects of the semi-vegetarian diet with infliximab for inducing remission in CD (n = 44) found that 100% achieved symptomatic remission in per-protocol analyses, with significant reduction in CRP and mucosal healing achieved in 46% of cases.[32] A second study of the semi-vegetarian diet and infliximab as first-line therapy for achieving remission demonstrated a high remission rate (76%; n = 17), low colectomy rate (6%), a significant decrease in CRP and erythrocyte sedimentation rate (ESR) at week 6 (9.42 mg/dl to 0.33 mg/dl, and 59 mm/hour to 17 mm/hour, respectively), and low 1-year remission rate (25%) and no additional colectomy cases.[33] Most (77%) patients with mild UC or UC in remission who received hospital-based dietary education had an improvement in symptoms at 2 weeks, and relapse rates were lower than those reported for medication over a median 3.6-year follow-up.[34] In a different cohort, patients with mild to severe active UC treated with the semi-vegetarian diet had a cumulative relapse rate of 14% at 1- and 27% at 5-year follow-up, considerably lower than those reported with conventional therapy (about 50% at 1 year).[35]

A diet low in sulphur-containing amino acids, particularly from red meat, dairy products and eggs, has been proposed to play a role in the development and progression of IBD by increasing the intestinal concentration of hydrogen sulphide and impairing butyrate synthesis.[36,37,38,39] Possible adverse reactions to sulphite food preservatives E220–E228 also deserve consideration.[40] Meat is an important contributor to sulphide generation by bacteria in humans.[41] However, this theory is controversial as hydrogen sulphide has also demonstrated gastroprotective effects.[42] Similarly, experimental studies of sulphur-containing amino acids are equivocal. Methionine may contribute to IBD pathogenesis at high dietary intakes;[43] however, several studies have demonstrated gastroprotective effects of methionine and other sulphur-containing amino acids.[44] Interestingly, hydrogen sulphide production may be independent of dietary sulphate and suppressed by prebiotic fibre.[45]

A prospective study of patients with UC in remission found that higher consumption of meat, especially red and processed meat, total protein, sulphur and sulphate were associated with disease relapse when compared with lower intakes.[46] Also, a small uncontrolled pilot study assessing a low-sulphur diet [avoiding eggs, cheese, whole milk, ice-cream, mayonnaise, soya milk, mineral water and sulphite-containing drinks (wine and cordials), nuts, cruciferous vegetables, and red meat] in patients with UC suggested better maintenance of remission after 56 months versus medication with evidence of marked histological improvement, reduced number of bowel movements (from 6 to 1.5 per day) and reduced medication requirement.[47] Additional evidence from semi-vegetarian diet studies discussed above suggests that a vegetarian or semi-vegetarian diet may be a feasible approach, but whether it is due to restriction of dietary sulphur or some other factor(s) is unclear.[48] Dietary changes used in these studies are complex, and attributing their effects to a simple mechanism such as reduced sulphur intake may be overly simplistic and difficult to substantiate.

The IBD-AID

A multi-component, multi-functional IBD-targeted diet simplistically termed the anti-inflammatory diet (IBD-AID) was developed for the treatment of IBD, and has some evidence to suggest it is an effective regime. The aim of the diet is to induce and maintain remission, and it restricts the intake of lactose, and refined or processed carbohydrates. Foods include soluble fibre, leeks, onions and fermented foods, red meat is replaced with fish high in omega-3 fatty acid content and chicken, olive oil is used in cooking and coconut oil in baking. The diet is also personalised to account for nutritional deficiencies and food intolerances, and stages the textures of the foods to improve absorption of nutrients and minimise intact fibre depending on the symptomology of the patient. In a case series report, 60% of patients with UC and CD treated with IBD-AID had either a good or very good clinical response after reaching compliance with a large reduction in symptoms scores, and all patients could discontinue at least one of their prior IBD medications.[49] In a subsequent clinical study, patients with CD were randomised to IBD-AID plus prebiotic fructooligosaccharides (FOS), FOS alone, or a placebo and control diet. The subjects were followed until either they had a flare or for up to 12 months. No subject flared in the IBD-AID group, while 31% flared in the FOS group, and 21% flared in the placebo group. There was a trend for longer survival without flare in the diet intervention group, and examination of the 16S rDNA sequencing data demonstrated significant increases in the mean abundance of the beneficial gut bacteria Roseburia after the diet intervention.[50]

The autoimmune protocol (AIP) diet

An AIP diet developed for IBD management was tested in patients with UC and CD. The aim of the diet was to reduce intestinal inflammation, dysbiosis and/or symptomatic food intolerance, and the regime consisted of a 6-week elimination phase (staged elimination of grains, legumes, nightshades, dairy, eggs, coffee, alcohol, nuts and seeds, refined/processed

sugars, oils and food additives) followed by a 5-week maintenance phase (during which no food group reintroduction was allowed). Nutritional deficiencies in iron and vitamin D were also treated with supplementation. Clinical remission was achieved by week 6 by 11/15 (73%) of study participants, and all 11 maintained clinical remission during the maintenance phase of the study. At the end of the study period, symptom scores, quality of life and faecal calprotectin were all significantly reduced, and endoscopic improvements were noted in those who underwent follow-up endoscopy. However, CRP did not significantly change during the study, and two participants with CD with ileal strictures developed either worsening disease activity or partial small bowel obstruction.[51,52] Overall, this study suggests potential benefits in UC, but the benefit and safety in CD is uncertain.

Personalised elimination diets

The use of empirical elimination re-challenge diets to identify food intolerances and construct a personalised exclusion diet has been well studied in CD.[53] Typically the re-challenge phase is preceded by induction of remission with an elemental diet (a liquid nutritional formula providing essential nutrients and hypo-allergenic protein as free amino acids). In one such study, 84% of patients with active CD achieved clinical remission within 14 days of commencing an elemental diet, and were then assigned to either glucocorticoids or an elimination re-challenge diet (reintroduction of foods). Remission lengths were significantly greater in the diet group (3.8 versus 7.5 months), with 45% remaining disease-free for at least 2 years.[54]

Immunoglobulin G (IgG) antigens against foods have been reported to be significantly higher in patients with CD than in healthy controls, and IgG-based testing has been used with some success as a guide for an elimination diet in patients with CD.[55,56] A 6-week intervention study in patients with CD found improvements in stool frequency, abdominal pain, general well-being and IFN gamma secretion of T-cells when compared with a sham diet.[57] In another study, 90% of patients with CD reported symptomatic improvement, with a reduction in inflammatory biomarkers and IgG titres for the excluded foods.[58] More recently, treatment of CD with an IgG-based exclusion diet resulted in significant improvements in symptoms and a reduction in faecal calprotectin in those with more severe disease.[59] This approach may help maintain remission, with an IgG-based exclusion diet resulting in better control of inflammatory biomarkers and a disease relapse rate of 12.5% versus 25% in controls.[60]

In one study of patients with UC, an IgG-based exclusion diet for 6 months significantly reduced symptoms scores, resulted in greater reduction in extraintestinal complications, greater improvements in body composition and albumin, and improvements in quality of life when compared with a control group.[61] Although most research of IgG-based exclusion diets has been in patients with CD, this report suggests a potential benefit for UC that requires further investigation.

Gluten-free diet for non-coeliac gluten sensitivity and coeliac disease

Non-coeliac gluten sensitivity (NCGS) may be more frequent in patients with IBD and could contribute to disease activity, although more research is needed to clarify the role of gluten-free diets. A majority (65.6%) of patients with IBD who have initiated a gluten-free diet independent of a diagnosis of coeliac disease report symptom improvement, and nearly 40% report fewer disease flare-ups.[62] In patients with IBD, NCGS has been shown to be more frequent than in irritable bowel syndrome (IBS) and dyspeptic controls, and has been associated with more severe clinical symptoms and stricturing disease.[63] Of relevance, NCGS may be related to an autoimmune phenotype with higher proportions of patients developing autoimmune disorders, positive for antinuclear antibodies, and with DQ2/DQ8 haplotypes compared with patients with IBS.[64] In a case report, a patient with severe treatment-resistant UC and absence of coeliac disease achieved full clinical remission (including severe bloody diarrhoea) and improvement in laboratory data (including ESR) within 12 weeks of a gluten-free diet, with symptom exacerbation on subsequent exposure to gluten that again resolved with a gluten-free diet.[65]

Patients with coeliac disease have been reported to have a three–10 times higher prevalence of IBD compared with those without coeliac disease in some studies.[66,67,68] Currently there are no prospective controlled studies of a gluten-free diet for patients with IBD with coeliac disease.[69] However, several case reports have described important clinical improvements in patients with IBD and coeliac disease treated with a gluten-free diet and medication.[70,71,72,73,74] The presence of coeliac disease should be ruled out, and in cases of confirmed coeliac disease a gluten-free diet should be initiated.

Additive-free diets

Industrial food additives such as bulking agents, colourings, emulsifiers, enzymes, flavour enhancers, preservatives, stabilisers and sweeteners have been suggested to play an important role in the development of autoimmune diseases including IBD.[75] In experimental studies, several food additives have been linked to alterations in the gut microbiome, intestinal inflammation and/or the development of IBD, including the emulsifiers polysorbate-80 and carboxymethylcellulose,[76,77,78] the thickener carrageenan,[79] non-caloric artificial sweeteners including sucralose,[80] acesulfame potassium[81] and saccharin,[82] the polysaccharide maltodextrin,[83] the whitener and anti-caking agent titanium dioxide[84], ethylenediaminetetraacetate (EDTA)[85], and the widely-used (yet typically undisclosed on product labels) enzymes, microbial transglutaminases.[86] Dietary exposure to such additives, in particular maltodextrin and carrageenan, has been estimated to be frequent in children with CD, although this was not related to disease severity.[87] A carrageenan-free diet has been examined in patients with UC in remission. The study had two arms, a carrageenan-free diet with either placebo capsules or carrageenan capsules (200 mg/day), to tease out the effects of carrageenan exposure. Despite being a relatively small study group of 12 people, and the carrageenan capsules providing less than average daily dietary exposures, the results were striking. At the end of the study, three patients who received carrageenan-containing capsules relapsed, while none of those who received placebo-containing capsules had a relapse. And laboratory tests showed increases in the inflammatory markers interleukin (IL)-6 and faecal calprotectin in the carrageenan-exposed group, but not in the placebo group.[88] Although evidence for adverse effects of carrageenan are limited, so too are safety data, and avoiding or eliminating exposure to this food additive would be advised in general.[89]

A diet containing low levels of oxides of titanium, aluminium and/or silicon was found to accelerate disease remission in patients with CD treated with corticosteroids in a pilot study.[90] However, a subsequent large, multi-centre, double-blind trial failed to replicate these findings.[91] More investigation is needed to clarify their contribution to IBDs.[92]

Maltodextrin is estimated to be found in about 60% of all packaged food products, with most people consuming foods containing maltodextrin at least twice a day.[93] Experimental evidence suggests that maltodextrin impairs defences against pathogenic gut bacteria, and increases the proximity of such bacteria to the epithelium.[94] Importantly, analysis of mucosa-associated bacteria in people with CD showed increased prevalence of a gene essential for maltodextrin metabolism.[95] However, clinical trials of maltodextrin-free diets are lacking.

In one study of 18 patients with CD, a 6-week organic diet low in 'environmental factors' such as fertilisers, pesticides, preservatives

and food additives was found to result in significant improvements on either magnetic resonance imaging or endoscopy evaluation as well as sonography in patients with CD when compared with a control diet based on the same non-organically produced foods. However, disease activity scores were similar to the control group.[96]

Specific carbohydrate diet (SCD)

Originally developed for the management of coeliac disease symptoms in the 1950s,[97] the SCD was popularised with the book 'Breaking the Vicious Cycle' in the 1980s for the management of IBD.[98] The original premise for the diet was that restriction of complex carbohydrates and refined sugar from the diet would prevent malabsorption and symptom development, later the hypothesis was expanded to include the idea that malabsorbed carbohydrates could cause bacterial dysbiosis and contribute to the intestinal inflammation of IBD. Research partially supports this theory with the finding that the microbiome of patients with IBD following the SCD may become more biodiverse and characterised by higher levels of anti-inflammatory bacteria.[99,100] The SCD is a modified carbohydrate diet that excludes disaccharides and most polysaccharides, but allows consumption of monosaccharides. The diet is also supplemented with homemade yogurt.

Numerous case reports suggest important clinical benefits of the SCD in paediatric patients with IBD.[101,102] For example, in paediatric CD treatment with the SCD for an average of 14 months, clinical symptoms were resolved, and laboratory indices were improved or normalised, including serum albumin, CRP, haematocrit and stool calprotectin.[103] Also in an adult woman with UC refractory to medication, the SCD diet improved symptoms within 3–6 months and resulted in remission, determined through colonoscopy, within 2 years.[104]

In the first prospective clinical study of the SCD, nine children with CD were enrolled in dietary treatment over a 12-week period, then continued the programme for up to 52 weeks. Within the first 12 weeks there was a significant clinical and mucosal improvement, with seven of the children (60%) achieving clinical remission by 12 weeks. Sustained clinical remission was seen in six of the seven patients who remained on the diet for 52 weeks.[105] A subsequent 12-week study in paediatric patients with active CD compared a SCD diet with more flexible versions; a modified SCD with oats and rice (MSCD); or a whole-food diet (WF) eliminating wheat, corn, sugar, milk and food additives. All the diets were associated with 100% clinical remission and reductions in CRP and ESR, although reductions in these inflammatory biomarkers were greater in the SCD and MSCD groups, and all patients had changes in their microbiome.[106]

In adults with CD, an intervention trial comparing the SCD with the MED-DIET found similar clinical and inflammatory biomarker responses. Symptomatic remission at week 6 was 46% versus 43%, faecal calprotectin response was 34% versus 30%, and CRP response was 5% versus 3% for the SCD versus MED-DIET, respectively, suggesting that the MED-DIET, because it is less restrictive, may be preferred to the SCD with mild–moderate CD.[107]

Low-FODMAP diet

A diet low in fermentable oligosaccharides, disaccharides, monosaccharides and polyols (low-FODMAP diet) has been investigated in IBD, primarily for relief of IBS-like symptoms. In patients with IBS-like symptoms and IBD, either in remission or mild–moderate disease, a 6-week low-FODMAP diet significantly reduced IBS symptom scores and improved IBD-related quality of life.[108] A 6-week low-FODMAP diet was found to reduce IBD disease activity scores and reduce faecal calprotectin in patients with mild IBD or IBD in remission.[109] However, a subsequent clinical trial found improvement in IBS symptom scores but no reduction in inflammatory biomarkers.[110]

Review
Inflammatory Bowel Disease: Towards a Model for Personalised Nutritional Therapy

Genotype-guided diet

Genotype-guided personalised nutrition may have relevance in IBDs, with some evidence to suggest certain gene variations may be associated with food intolerance, and also help guide dietary interventions and nutritional supplementation.[111] Regarding food intolerances, patients with CD without the GSTT1 (–/–) variant of the GST gene were found to be less likely to tolerate the brassica vegetables broccoli, cauliflower and Chinese greens in a cohort from Auckland, New Zealand.[112] In the same cohort, patients carrying the G allele of FOXO3 were found to be less likely to tolerate mustard, wasabi, and raw and cooked tomatoes.[113] Those with the rs1050152 variant of the organic cation transporter gene OCTN1 were found to be significantly more likely to be intolerant to mushrooms.[114] Genetic lactase persistence as indicated by the T allele of rs4988235, the gene encoding for lactase-phlorizin hydrolase (lactase), had a higher risk of CD.[115] As these studies were carried out in a unique cohort from New Zealand, it is important to emphasise that the same results may not always apply to other populations.[116]

Functional foods

In addition to more complex dietary changes, the addition of certain foods to the diet of patients with IBD has been shown to reduce disease severity. Patients with UC who added 600 g of salmon per week to their usual diet for 8 weeks had significantly reduced symptoms scores and a tendency of decreased levels of CRP.[117] Patients with UC who consumed bilberries equivalent to 600 g a day of fresh berries for 9 weeks had a 90% treatment response, a 63% remission rate, a significant decrease in faecal calprotectin, and in colonic biopsies reduced pro-inflammatory and enhanced anti-inflammatory cytokines.[118,119] The addition of 60 g of oat bran daily to the diet of patients with UC for 4 weeks increased stool butyrate concentration by 36%, and reduced symptoms of abdominal pain and reflux.[120] Also, 50 ml of olive oil daily for 20 days decreased the inflammatory markers CRP and ESR, and improved gastrointestinal symptoms in patients with UC.[121]

Micronutrient deficiencies and therapy

Nutritional deficiencies are commonly associated with IBD, especially deficiencies in vitamins A, C, D, K, B3, B6, B12, folate, magnesium, calcium, iron, selenium, zinc and copper.[122,123] Medications can further contribute to deficiencies, for example corticosteroid therapy reduces absorption of calcium in the intestine,[124] and sulfasalazine and methotrexate increase folate requirement.[125] Although micronutrient deficiencies may not be associated with overt clinical symptoms of deficiency-related disease (e.g. scurvy), they are associated with extraintestinal complications, including anaemia, bone disease, cardiovascular complications, impaired wound healing and colorectal cancer risk.[126] Supplementation with micronutrients is not only important for treating deficiencies, in some cases micronutrients may help to reduce disease activity and maintain remission.[127] Although several experimental studies suggest important effects of various micronutrients on colonic inflammation in IBD, human studies exploring the effects of micronutrients on disease activity are limited.[128]

Vitamin D deficiency is prevalent in the general population, and is 3.2 times higher in patients with IBD.[129] Vitamin D treatment may help reduce disease activity and maintain remission. A randomised placebo-controlled trial of 1200 IU (30 µg) of vitamin D3 daily in patients with CD showed improvement in serum 25(OH) levels after 3 months, and more than 50% lower rate of relapse compared with placebo.[130] Patients with CD treated with 1000 IU (25 µg) per day of vitamin D3 for 6 weeks had a reduction in disease activity scores and CRP.[131] Supplementation with up to 5000 IU (125 µg) per day of vitamin D3 for 24 weeks raised serum 25(OH)D3, and reduced disease activity scores and improved quality of life scores.[132] Notably, most patients required the maximum allotted 5000 IU of daily cholecalciferol to reach a serum 25(OH)D level of 40 ng/ml. Similarly, a clinical trial comparing a high [10 000 IU/day

(250 µg)] with a low dose (1000 IU) suggested a higher dose was necessary for optimising blood levels and maintaining remission in patients with CD.[133] Interestingly, clinical trials in patients with IBD suggest vitamin D treatment reduces ESR, high-sensitivity (hs)-CRP and TNF-α, increases cathelicidin (a precursor to an antimicrobial protein) gene expression, and increases gut bacterial diversity.[134,135,136]

Zinc has been shown to improve disease outcomes, reduce intestinal permeability and help to maintain remission. In patients with CD and UC, correction of zinc deficiency was associated with better disease outcomes, including a decrease in hospitalisations and disease-related complications compared with subjects who remained zinc deficient, over a 12-month period. Furthermore, patients with CD who normalised their zinc levels had a significant reduction in risk of subsequent surgeries.[137] In patients with CD in remission, supplementation with 25 mg of zinc three times daily for 8 weeks reduced intestinal permeability and relapse rate over a 12-month follow-up period.[138] Patients with active UC or ulcerative proctitis who were treated with 50 mg of zinc three times per day or placebo for 4 weeks as an adjuvant to drug therapy showed evidence of a modest improvement in clinical symptoms when compared with placebo, although this was not statistically significant.[139] The doses used in these studies may be unnecessary, with doses > 40 mg daily from food and supplements associated with copper deficiency and gastrointestinal side-effects.[140]

Thiamine may be useful for reducing fatigue in patients with IBD. Supplementation with 600 mg (for 60 kg adults) to 1500 mg (90 kg adults) of thiamine daily for 20 days completely alleviated symptoms of fatigue in 10 out of 12 subjects with UC and CD, and the remaining two also reported a significant improvement.[141] Notably there was an absence of blood thiamine deficiency, suggesting that conventional measurement may be insufficient for detecting deficiency, higher metabolic requirements or predicting treatment response. At this dose, thiamine may also be working as a pharmacological compound rather than to improve functional sufficiency.

Riboflavin has been found to have anti-inflammatory and antioxidant effects in CD. In an exploratory clinical trial, patients with CD of varying disease activity received 100 mg riboflavin for 3 weeks. Riboflavin supplementation was associated with reductions in the inflammatory biomarkers CRP, ESR, platelets and IL-2, an antioxidant effect indicated by an increase in the concentration of plasma free thiols, a reduction in clinical symptoms and an improvement in quality of life.[142]

Probiotics and prebiotics

Probiotics have been the subject of considerable research in IBD but, despite a strong theoretical basis for their use, clinical studies have provided sparse and conflicting evidence, with meta-analyses and systematic reviews generally concluding that there is little evidence for efficacy in CD, modest and inconsistent data for UC, and good support for probiotics in pouchitis.[143] All the clinical trials identified by the author are listed in Table 1. There is considerable heterogeneity in probiotic clinical trials related to probiotic strains, dose, duration and clinical outcomes (Table 1).

Table 1: Clinical trials of probiotics, synbiotics and fermented foods in IBD

Probiotic strain(s)	Dose	Duration	Subjects	Findings	References
Escherichia coli Nissle 1917	25 billion CFU daily	12 months	Active CD	Trend toward reduced relapse rate	Malchow *et al.* (1997)[144]
Escherichia coli Nissle 1917	25 billion CFU daily	12 months	Remission UC	Equivalence to mesalazine in remission	Kruis *et al.* (2004)[145]
Escherichia coli Nissle 1917	25 billion CFU daily	12 months	Remission UC	Equivalence to mesalazine in remission	Rembacken *et al.* (1999)[146]
Saccharomyces boulardii	1 g daily	6 months	Active CD	Significant reduction in relapse rate	Guslandi (2000)[147]
Saccharomyces boulardii	1 g daily	12 months	Active CD	No significant reduction in relapse rate	Bourreille *et al.* (2013)[148]
Saccharomyces boulardii	600 mg daily	3 months	Remission CD	Reduction in intestinal permeability	Garcia Vilela *et al.* (2008)[149]
Bifidobacterium longum plus inulin/oligofructose mix	200 billion CFU/6 g daily	6 months	Active CD	Significant improvement in CDAI scores	Steed *et al.* (2010)[150]
Lactobacillus rhamnosus GG	2 billion CFU daily	6 months	Active CD	No significant reduction in relapse rate	Shultz *et al.* (2004)[151]
Lactobacillus rhamnosus GG	20 billion CFU daily	up to 2 years	Active CD	No significant reduction in relapse rate	Bousvaros *et al.* (2005)[152]
Lactobacillus rhamnosus GG	18 billion CFU daily	12 months	Remission UC	Significant maintenance of remission	Zocco *et al.* (2016)[153]
Multi-strain (VSL#3)	720 billion CFU daily	12 weeks	Active UC	Significant achieved remission	Sood *et al.* (2009)[154]
Multi-strain (VSL#3)	720 billion CFU daily	8 weeks	Active UC	Significant reduction in disease activity	Tursi *et al.* (2010)[155]
Bifidobacterium longum 536	300 billion CFU daily	8 weeks	Active UC	Significant reduction in disease activity	Tamaki *et al.* (2016)[156]
Bifidobacterium breve plus galacto-oligosaccharides	1 billion CFU/ 5.5 g daily	12 months	Active UC	Improvement of endoscopic score	Ishikawa *et al.* (2011)[157]
Bifidobacterium breve, Lactobacillus casei, Bifidobacterium longum plus psyllium	75 billion/ 9.9 g daily	12 months	Active CD	Reduced disease activity and enhanced remission	Fujmori *et al.* (2007)[158]
Lactobacillus acidophilus La-5 and ***Bifidobacterium animalis*** subsp. lactis BB-12	150 billion CFU daily	12 months	Remission UC	No significant reduction in relapse rate	Wildt *et al.* (2011)[159]

Multi-strain (Symprove)	10 billion CFU/50 ml daily	4 weeks	Remission CD and UC	Reduction in faecal calprotectin UC only, no reduction in symptoms	Bjarnason *et al.* (2019)[160]
Lactobacillus salivarius, Lactobacillus acidophilus and ***Bifidobacterium bifidus*** BGN4	Not specified	2 years	Active UC	Reduced disease activity	Palumbo *et al.* (2016)[161]
Multi-strain plus fructo-oligosaccharides	3 billion CFU/225 g daily	8 weeks	Active UC	Reduced disease activity	Kamarlı Altun *et al.* (2019)[162]
Bifidobacteria fermented milk	10 billion CFU/ 100 ml daily	12 months	Remission UC	Significant maintenance of remission	Ishikawa *et al.* (2003)[163]
Kefir (fermented dairy)	20 billion/ 400 ml	4 weeks	Remission/ active CD and UC	Reduced disease activity in CD only	Yilmaz *et al.* (2019)[164]

CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CFU, colony-forming unit; UC, ulcerative colitis.

Overall, some species of probiotics have evidence of clinical efficacy in UC with less compelling data for CD, and they may be more appropriate for maintenance of remission than treatment of active disease.[165] Importantly, probiotics should be used with caution with immune-suppressant drug use, long-term corticosteroid treatment, damaged intestinal mucosa or in immunocompromised patients.[166] In active severe IBD with mucosal disruption, probiotics may be contraindicated as cases of bacteremia have been reported.[167,168]

Thus, probiotic safety is better established in less severe disease activity or IBD in remission.[169]

Prebiotics have considerable experimental evidence to suggest that they could modify microbial composition and lower inflammation in IBD; in contrast, clinical studies are few but generally suggest that prebiotics are well tolerated and can improve bacterial composition and reduce disease activity in UC particularly.[170] The author lists all the clinical trials that they could identify in Table 2. Clinical trials of prebiotics have generally used doses of > 10 g/day for > 4 weeks (Table 2).

Table 2: Clinical trials of prebiotics and prebiotic fibres in IBD

Prebiotics	Dose	Duration	Subjects	Findings	References
Lactulose	10 g daily	4 months	Active CD and UC	No clinical benefits	Hafer *et al.* (2007)[171]
Fructo-oligosaccharides	15 g daily	3 weeks	Active CD	Reduction in disease activity	Lindsay *et al.* (2006)[172]
Oligofructose/inulin	7.5 or 15 g daily	9 weeks	Active UC	Reduction in disease activity with 15 g	Valcheva *et al.* (2019)[173]
Oligofructose/inulin	12 g daily	2 weeks	Active UC	Significantly decreased dyspeptic symptoms and calprotectin	Casellas *et al.* (2007)[174]

with mild–moderate UC, butyrate (4 g/day)

Oligofructose/inulin	15 g daily	4 weeks	Active CD	No clinical benefits, worse abdominal pain	Benjamin *et al.* (2011)[175]
Germinated barley foodstuff	20–30 g daily	4 weeks	Active UC	Significant reduction in symptoms	Bamba *et al.* (2002)[176]
Germinated barley foodstuff	20–30 g daily	4 weeks	Active UC	Significant reduction in symptoms	Kanauchi *et al.* (2002)[177]
Psyllium	10 g twice daily	4 months	Remission UC	Significant reduction in symptoms	Hallert *et al.* (1991)[178]
Psyllium	10 g twice daily	12 months	Remission UC	Equivalence to mesalazine in remission	Fernández-Bañares *et al.* (1999)[179]
Oat fibre	60 g oat bran (corresponding to 20 g dietary fibre)	3 months	Remission UC	Increased faecal butyrate, fewer gastrointestinal symptoms, no relapse	Hallert *et al.* (2003)[180]
Human milk oligosaccharide (2′-fucosyllactose)	2 g daily in a multi-component nutritional formula	6 weeks	UC (activity not specified, n = 4), IBS, coeliac disease	Improved quality of life	Ryan *et al.* (2021)[181]
Galactooligosaccharides	2.8 g daily	6 weeks	Active UC	Improvement for some symptoms, but no effect on clinical scores or inflammation	Wilson *et al.* (2021)[182]

CD, Crohn's disease; IBS, irritable bowel syndrome; UC, ulcerative colitis.

Overall, the clinical evidence suggests some prebiotics may be useful, primarily for UC, while others may not be effective, and some could worsen symptoms. Oligofructose/inulin > 12 g daily, and psyllium (Plantago ovata) husks have more compelling evidence, with the psyllium having considerable research for gastrointestinal disorders in general to support its safety and use.[183] Germinated barley foodstuff may also be useful, but the presence of gluten should be considered against the role of coeliac disease and NCGS in IBDs. Practical considerations are summarised in Table 3.

Butyrate

Butyrate is an endogenously produced short-chain fatty acid that plays a major role in the physiology of the colonic mucosa. In IBD, butyrate metabolism may be impaired, and may contribute to mucosal barrier dysfunction and inflammation.[184,185,186] Enteric-coated sodium or calcium butyrate salts have been used with some success in IBD.[187] In patients with mild–moderate UC who were poorly responding to mesalazine treatment, the addition of 921 mg butyrate and 750 mg inulin resulted in a marked improvement of symptoms and in the endoscopic appearance of mucosa.[189] The addition of butyrate to mesalazine in active UC for 28 days resulted in 85% experiencing a significant improvement in rectal bleeding and stool frequency compared with 55% with mesalazine alone. The butyrate group also had an increase in their faecal butyrate-producing bacteria pool, and reduced elevated baseline Bacteroides fragilis/ Faecalibacterium prausnitzii ratio and lowered serum inflammatory biomarkers.[190] In patients with CD with mild–moderate disease activity who took butyrate (4 g/day) for 4 weeks, 69% responded to treatment with 53% achieving remission. Further, endoscopical and plus mesalazine for 6 weeks reduced disease histology and symptoms scores better than mesalazine alone.[188] Similarly, in patients

histological scores significantly improved, and inflammatory biomarkers were reduced.[191]

N-acetylglucosamine

N-acetylglucosamine (NAG) is an amino sugar and component of epithelial cells and mucus membranes of the digestive tract.[192] Experimentally, NAG has been shown to reduce intestinal inflammation and modulate the systemic immune system in autoimmunity.[193,194] Metabolism of amino sugars may be impaired in patients with IBD, but NAG appears to bypass this metabolic impairment and be preferentially incorporated into the intestinal mucosa.[195]

Clinical studies suggest that NAG may be useful. Treatment-resistant paediatric patients with IBD were given 3–6 g per day of NAG as an adjuvant to usual therapy, in addition to rectal administration in some children. Both oral and rectal administration of NAG resulted in clear clinical and endoscopic or radiological improvement.[196] In adults with IBD, treatment with 6 g NAG orally for 4 weeks resulted in an 88.1% response rate for overall clinical symptoms; a 58.8% response for abdominal pain with a 49% reduction in symptom score; a 64.7% response for diarrhoea with a 47% reduction in symptom score. There were also significant reductions in symptom scores for nausea, passage of mucus and rectal bleeding.[197]

Glutamine

Glutamine plays an important role in the integrity of the intestinal mucosa and regulation of the inflammatory response; however, despite its popularity as a dietary supplement for digestive health, the use of glutamine in IBD is controversial.[198] One study in patients with CD in remission found that glutamine (0.5 g/kg body weight) for 2 months reduced intestinal permeability and improved morphology.[199] However, other studies have not reported any benefit. Glutamine (21 g) for 4 weeks did not restore to normal the increased permeability seen in patients with CD, nor did it reduce disease activity or inflammatory biomarkers.[200] In children with CD, a glutamine-enriched polymeric (exclusive enteral nutrition) diet (8 g) for 4 weeks had no advantage over a standard low-glutamine polymeric diet for symptom reduction or reducing intestinal permeability, in fact symptom control was worse with glutamine.[201] Similarly, in adults with IBD, glutamine-enriched parenteral nutrition had no additional benefit.[202]

Creatine

The amino acid creatine is an energy precursor in the creatine kinase/phospho-creatine system, which is important for meeting the cellular energy demands of epithelial junction assembly and barrier integrity, and supplementation with creatine can restore energy synthesis and reduce disease activity in experimental models of colitis.[203] In a case report, a patient recently diagnosed with mild Crohn's ileitis started mesalamine and stopped taking a creatine supplement, after which symptoms progressively became more severe. The patient had noticed subjective improvement with creatine, they then stopped mesalamine and started creatine (1.5 g daily), after which symptoms significantly improved and mucosal healing was observed after 6 months of creatine monotherapy.[204] Subsequently it has been found that patients with IBD have lower levels of creatine messenger RNA compared with control.[205] The rationale for a clinical trial has been published with a suggested dose of 3–5 g twice daily.[206]

Phosphatidylcholine

Phosphatidylcholine is a major component of the mucus layer that forms a protective and functional barrier across the intestinal epithelium, is significantly reduced in IBD, and can be restored with phosphatidylcholine supplementation. Phosphatidylcholine comprises more than 90% of phospholipids in the mucus layer that prevents the invasion of bacteria into the intestinal epithelium from intestinal lumen, but in UC the mucus phosphatidylcholine content is reduced but as much as 70%.[207] Experimentally, phosphatidylcholine depletion via diminished luminal transport leads to low mucus phosphatidylcholine, bacterial invasion of the submucosa, inflammation and IBD-like symptoms that are reversed with phosphatidylcholine administration.[208]

Human clinical trials of delayed-release (acid-resistant) phosphatidylcholine formulations have demonstrated important clinical benefit in active and steroid-refractory UC,[209,210,211] inadequate response to mesalazine,[212] and for maintenance of remission (1–4 g daily).[213] A series of clinical trials of a different phosphatidylcholine formulation (differences in delayed-release technology and phosphatidylcholine %) failed to demonstrate significant clinical effect, but this has been attributed to the formulation. Earlier trials using the 30% phosphatidylcholine-containing lecithin in a delayed intestinal release formulation were found to improve clinical and endoscopic outcomes, histological activity and quality of life in patients with UC when trials of the different formulation were excluded from a meta-analysis.[214] Dose–response analysis has demonstrated that optimal benefit occurs at >1 g to 4 g daily.[213]

Coenzyme Q10

Coenzyme Q10 (CoQ10) or ubiquinone has shown promise in patients with mild–moderate UC. In a clinical trial, a patient with UC who received CoQ10 (200 mg daily) for 8 weeks had a significant reduction in symptom scores and blood pressure, and an improved quality of life compared with placebo.[215] It was also found that CoQ10 treatment reduced inflammatory biomarkers IL-17 and nuclear factor (NF)-κB, increased serum levels of the anti-inflammatory cytokine IL-10, and increased levels of the anti-microbial peptide cathelicidin.[216] Although the use of CoQ10 in UC is novel, a previous study in patients with functional gastrointestinal disorders also found an improvement in bowel movement frequency and quality of life with 150 mg of CoQ10 (as ubiquinol) daily.[217] Gastroprotective effects in experimental models of colitis have also been observed.[218,219]

Omega-3 polyunsaturated fatty acids

The omega-3 polyunsaturated fatty acids, especially, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have undergone considerable research in IBD, but despite several clinical trials exploring potential therapeutic effects the outcomes have been mixed. Poor clinical outcomes and null effects have been observed in some studies; however, others have found modest but clinically important benefits such as improved gut histology, decreased disease activity, reduced requirement of corticosteroids and lower rates of relapse.[220] A potential explanation for conflicting evidence of benefit is problems in study design, with two interesting possibilities being that dietary omega-3 to omega-6 ratio could impact treatment response, or that treatment could be personalised to people with biomarkers of inflammation.[221]

Supporting these possible limitations, an interesting clinical study examined the effect of 500 mg daily of EPA in patients with UC in remission, but with high elevated faecal calprotectin (≥ 150 µg/g). After 6 months, 63% of the intervention group had a 100-point reduction in faecal levels of calprotectin compared with 13.3% with placebo, and sustained clinical remission was achieved by 63.3% of patients versus 13.3% in the placebo group.[222] Also, a dietary intervention that modified the omega-3 to omega-6 ratio with foods, achieving about 1700 mg/day from EPA and DHA, plus supplementation of 7 ml/day of perilla oil, providing about 3400 mg/day of alpha-linoleic acid was able to show a significant association between higher omega-3 to omega-6 ratio and maintenance of remission in patients with UC and CD.[223] Omega-3 polyunsaturated fatty acids may be a useful addition to therapy, but could benefit from personalisation to inflammatory biomarkers (e.g. elevated faecal calprotectin) and may be more effective with improvement in dietary omega-3 to omega-6 ratio. The omega-3-index (erythrocyte EPA/DHA %) corelates

well with dietary EPA/DHA incorporation in gastrointestinal tissues, and may be a useful biomarker for personalising EPA/DHA therapy.[224]

Curcumin

Curcumin is a safe and effective therapy for improving maintenance of remission of UC when given as adjunctive therapy along with mesalamine or sulfasalazine.[225] Curcumin may also help reduce acute disease activity. In an open label study, patients with active IBD were treated with 1080 mg curcumin daily for 1 month and then 1440 mg daily for the remaining 2 months. All patients with proctitis improved, and four out of five patients with CD had lowered symptom scores and ESR.[226] Patients with UC who received curcumin, 1 g after breakfast and 1 g after the evening meal, plus sulfasalazine or mesalamine for 6 months had a lower rate of relapse (4.65%) compared with medication and placebo (20.51%), as well as lower symptom and endoscopic scores.[227] Patients with active UC who were not responding adequately to mesalamine were given 3 g of curcumin daily for 4 weeks. Curcumin was superior to placebo and mesalamine in inducing clinical and endoscopic remission.[228] Notably, a low dose of 450 mg curcumin daily was ineffective in inducing remission in mild–moderate UC.[229]

Boswellia

Frankincense *(Boswellia serrata)* has been used for centuries as a traditional medicine to treat inflammatory disorders, with some evidence to suggest it may help induce remission in IBD.[230] Patients with active UC who were given 1050 mg Boswellia gum resin daily for 6 weeks achieved a better rate of remission (82%) than sulfasalazine (75%).[231] Similarly in patients with chronic colitis, 900 mg Boswellia gum resin daily for 6 weeks was also found to be superior to sulfasalazine for induction of remission, with rates of 70% and 40%, respectively.[232] In patients with collagenous colitis and chronic diarrhoea, monotherapy with 1200 mg Boswellia gum resin daily for 6 weeks resulted in higher clinical remission (63%) compared with placebo (26%), but had no effect on histology or quality of life.[233] An enhanced bioavailability and potency extract of Boswellia (250 mg of Boswellia/lecithin complex) reduced minor symptoms, the use of drugs and medical consultation, and faecal calprotectin in patients with UC in remission.[234] In patients with CD in remission, however, Boswellia was not found to be more effective for preventing disease relapse than placebo.[235]

Resveratrol

Resveratrol has prebiotic, immune-modulating, anti-inflammatory and antioxidant activity, with clinical evidence to suggest it can reduce clinical progression of several autoimmune diseases, including IBD.[236,237] In patients with active UC, supplementation with 500 mg resveratrol for 6 weeks significantly reduced clinical symptom scores and the inflammatory biomarkers TNF-α and NF-κB when compared with placebo.[238] Resveratrol also improved oxidative/antioxidative status, with a significant reduction in malondialdehyde, and an increase in superoxide dismutase and total antioxidant capacity.[239]

Aloe vera

Aloe vera juice has been shown to influence gastrointestinal health via promoting mucosal tissue repair, prebiotic effect, enhancing digestion, increasing absorption of nutrients and reducing inflammation.[240,241,242] Treatment of 100 ml twice daily with aloe vera inner-leaf gel for 4 weeks in active UC was more effective in inducing remission (30%) than the placebo (7%). Aloe vera also significantly decreased disease activity and histological scores.[243]

Silymarin

Silymarin (Milk thistle extract) may be useful to help maintain remission in UC. In one study, patients who were in remission received either 140 mg silymarin or placebo once daily for 6 months along with their standard therapy. At the end of the study, 98% (n = 38) of the silymarin group maintained remission compared with 65% for placebo (n = 32). Silymarin also reduced clinical disease activity scores and improved haemoglobin and ESR when compared with placebo.[244]

Discussion

This review highlights a wide range of therapeutic diets and nutrient-based supplements that have potential usefulness in the integrative management of IBDs. Adjuvant nutritional therapies could be used with conventional care or could be considered as alternative treatments in cases of drug intolerance or treatment resistance. Because IBDs typically have a relapsing disease course, adjuvant nutritional therapies have promise as relatively safe interventions that could significantly contribute to disease control and improved quality of life.[245] The use of nutritional therapies as alternative treatment options requires more research to establish use but, as evidenced in this review, there is clearly promise for specific interventions. Additionally, it is notable that most nutritional interventions have been studied in isolation; however, in clinical nutrition practice combinations of therapies could be personalised, may have additive effects, and may be more likely to enhance disease control and remission

Important limitations of some nutritional therapies for IBD include a lack of suitably controlled interventions that could help inform clinical decision-making, especially in the case of dietary interventions. An example is the comparison of the SCD and MED-DIET, which both performed equally well despite the SCD being considerably more restrictive.[109] Pragmatically, an easier to follow diet would be preferable, but unless such comparisons are made it may be difficult to prioritise one dietary approach over another. Mixed treatment outcomes were also frequently identified for nutritional interventions, indicating further research is needed to better understand the efficacy of candidate therapies. In the case of nutrients, many studies consisted of traditional randomised-controlled trials; however, clinical trials of nutrients would benefit from trial designs that appreciate their differences from pharmacological therapies. Unlike drugs, nutrients tend to have lower effect sizes, are influenced by background dietary intake, have dose–response curves, and benefit from personalisation.[246] Nonetheless, despite these limitations, the formulation of clinical considerations based on nutritional therapies with more compelling evidence related to the therapeutic diets and nutrient-based supplements reviewed here could inform clinical application (Table 3).

Table 3: Clinical consideration of therapeutic diets and nutrient-based supplements for IBDs

Intervention	Discussion	Possible clinical application
Healthy diet	Unhealthful dietary practices could increase disease risk and severity. Minimally processed, semi-vegetarian, traditional dietary patterns can result in induction of remission and prevention of relapse.	Increase consumption of fresh fruits, vegetables, legumes and whole grains in line with dietary approaches such as the traditional Mediterranean-style diet. Limit red meat and include fish. Emphasise foods and food groups with prebiotic properties, such as fermented, high-fibre and phytonutrient-dense foods (e.g. natural yoghurt, fermented vegetables, root vegetables, green leafy vegetables, berries).
The IBD-AID diet	An AID developed for the treatment of IBD has been developed with some evidence to suggest it is an effective regime.	Consider the AID as a structured approached to personalising diet therapy in patients with IBD.
Personalised elimination diet	Elimination diets can help reduce symptoms by limiting exposure to foods that exacerbate inflammation.	An elimination diet can be based on food sensitivity testing, including IgG. Without testing, an elimination and re-challenge with major and/or suspected food allergens may still be useful.

NCGS	NCGS may be more frequent in patients with IBD, and could contribute to disease activity.	Consider a therapeutic trial with a gluten-free diet and re-challenge.
Coeliac disease	Coeliac disease has a significantly higher prevalence in IBD and should be ruled out with testing.	Coeliac disease can be treated with a gluten-free diet.
Additive-free diet	Experimental evidence suggests that industrial food additives may play an important role in the development of IBD, and a carrageenan-free diet may be effective.	Eliminate or reduce exposure to industrial food additives. A carrageenan-free diet could be trialled in select patients.
The SCD	Case reports and small preliminary clinical trials suggest important benefits of the SCD in patients with IBD, which may help induce and maintain remission.	The SCD could be considered in select patients, particularly treatment-resistant paediatric CD. The diet is restrictive and requires close professional supervision.
Increase intake of functional foods	Advise to increase intake of foods with anti-inflammatory effects, such as antioxidant- and omega-3 fatty acids-rich foods.	Advise patient to increase intake of polyphenol-rich fruits and vegetable foods and beverages, additionally increase intake of omega-3-rich foods, such as nuts, seeds, cold water fish and their oils, whole oats or oat fibre, and extra virgin olive oil.
Micronutrient deficiencies	Micronutrients deficiencies are widespread in IBD, and deficiencies can contribute to disease activity and co-morbidity.	A multivitamin and mineral supplement is a safe, inexpensive way to improve micronutrient intake. However, a multivitamin alone may not be sufficient to optimise intake, and laboratory screening for deficiency and to assess treatment response is recommended.
Vitamin D	Vitamin D treatment may help reduce disease activity and maintain remission.	Assessment of vitamin D status and subsequent supplementation in the case of deficiency. Higher doses of vitamin D [> 5000 IU (125 µg)] may be required to improve clinical symptoms and serum 25(OH)D3.
Probiotics	Some probiotic strains have shown benefit in mild–moderate IBD, and for maintaining disease remission.	Consider a probiotic supplement with demonstrated benefit in IBD. At least 2 months of treatment may be required to see benefit. If no response, another probiotic could be trialled. Avoid probiotics in severe, active IBD.
Prebiotics	Prebiotic supplements can help improve gut microbiota composition and may help maintain remission.	Consider supplementing with 10 g psyllium twice daily for at least 4 months in UC, and 15 g of FOS/inulin for at least 3 weeks in UC or CD.
Butyrate	Butyrate metabolism may be impaired, and contribute to mucosal barrier dysfunction and inflammation. Enteric-coated sodium or calcium butyrate salts have been used with some success in active IBD and to maintain remission.	Consider 4 g of enteric-coated or enhanced-delivery butyrate as an adjuvant to therapy in active IBD.
NAG	Experimentally, NAG has been shown to reduce intestinal inflammation and modulate the systemic immune system in autoimmunity.	Consider 6 g daily of NAG in active IBD.

Glutamine	The use of glutamine in IBD is controversial.	There appears to be no significant benefit of glutamine in IBD.
Creatine	Creatine may help maintain gut epithelial integrity, and a single case report suggests benefit.	Consider 3–5 g of creatine 1–2 times daily (experimentally, in the absence of trial data).
Phosphatidylcholine	Phosphatidylcholine incorporates in the protective mucus layer, and has been shown to reduce disease activity and help maintain remission.	Consider 1–4 g of enteric-coated or enhanced-delivery phosphatidylcholine daily in UC.
CoQ10	A preliminary clinical trial suggests CoQ10 may help reduce UC disease activity.	Consider a trial of 200 mg daily for at least 8 weeks.
Omega-3 polyunsaturated fatty acids	EPA/ DHA have conflicting evidence of efficacy, but may improve gut histology, decrease disease activity, reduce requirement of corticosteroids and lower rates of relapse.	Consider supplementation with fish oil, at least 500 mg EPA daily, especially if inflammatory biomarkers are elevated. Emphasise omega-3 polyunsaturated fatty rich-foods such as cold water fish and linseeds. Avoid omega-6 polyunsaturated fatty acids in processed foods, baked goods and vegetable cooking oils, instead using extra virgin olive oil (cooking) or coconut oil (baking) in certain sub-sections of patients with IBD. The omega-3-index may help personalise therapy.
Curcumin	Curcumin is a safe and effective therapy for improving maintenance of remission of UC when given as adjunctive therapy along with mesalamine or sulfasalazine.	Consider 2 g of curcumin or curcuminoids daily given in two divided doses.
Boswellia	Boswellia may help induce remission in active IBD.	Consider 900 mg of Boswellia gum resin for at least 6 weeks.
Resveratrol	Resveratrol may reduce clinical disease activity, and systemic inflammation and oxidative stress.	Consider 500 mg once daily, particularly if biomarkers of oxidative stress and inflammation are elevated.
Aloe vera	Aloe vera may promote mucosal tissue repair and reduce inflammation.	Consider 100 ml twice daily of aloe vera inner-leaf gel for 4 weeks.
Silymarin	Silymarin may help maintain remission and reduce ESR in UC.	Consider 140 mg silymarin or placebo once daily for 6 months.

AID, anti-inflammatory diet; CD, Crohn's disease; CoQ10, coenzyme Q10; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; ESR, erythrocyte sedimentation rate; FOS, fructooligosaccharides; IBD, inflammatory bowel disease; IgG, immunoglobulin G; NAG, N-acetylglucosamine; NCGS, non-coeliac gluten sensitivity; SCD, specific carbohydrate diet; UC, ulcerative colitis.

Some diets, including the AIP diet and genotype-guided diet, were excluded due to limitations in evidence. The low-FODMAP was excluded as it is for symptoms of IBS, not inducing and/or maintaining IBD remission.

Clinically, dietary interventions could be used in combination as part of rational decision-making with lower risk, higher likelihood of benefit dietary interventions forming part of a first-line dietary approach, while more personalised elimination diets could be considered on a case-by-case basis, and more demanding and restrictive interventions being reserved for treatment resistance (Figure 1).

Similarly, nutrient-based supplements with supportive evidence could be approached pragmatically, prioritising those generalisable across IBDs, then personalising based on IBD subtypes and potential clinical benefit (Figure 2).

Figure 1: Hypothetical approach to integrating different diets for IBD.

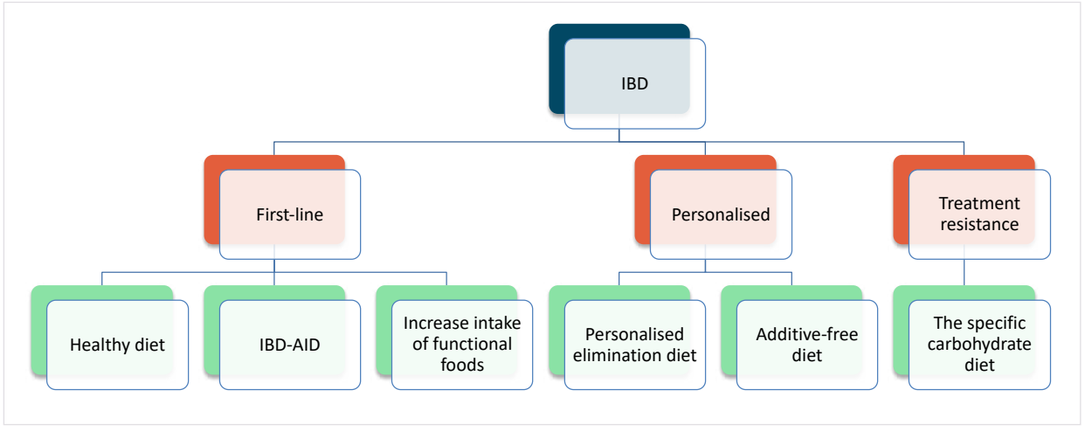
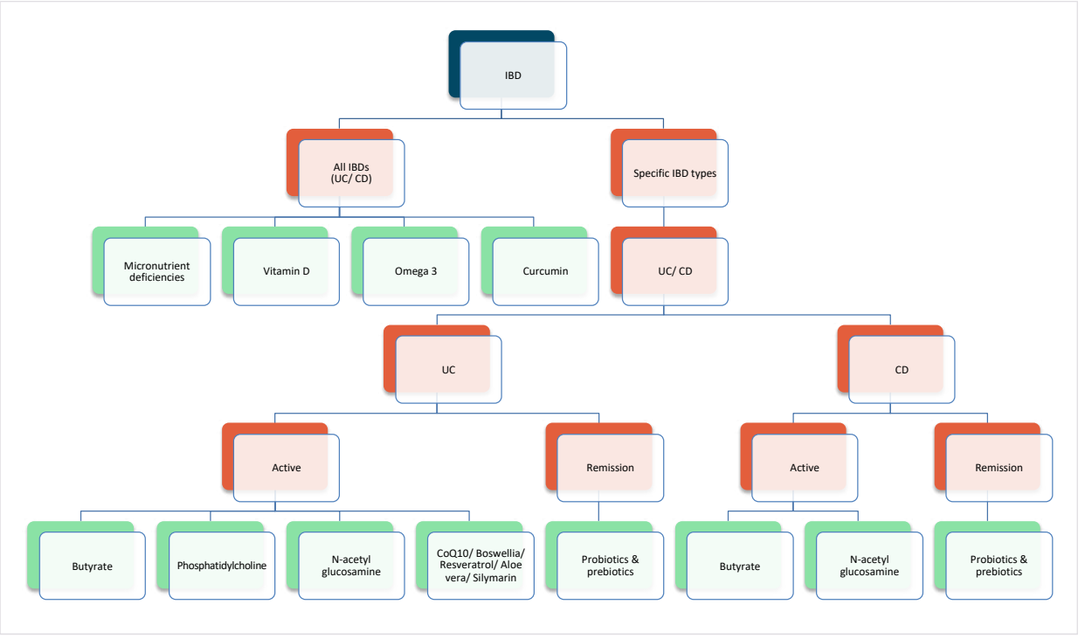


Figure 2: Hypothetical approach to integrating different nutrient-based supplements for IBD.



It must be emphasised that these are hypotheses, not guidelines, and several therapies are based on very limited research, preventing their routine use. The purpose of presenting nutritional therapies in this pragmatic, integrative model is to stimulate further investigation and research of multi-component, individualised clinical nutritional interventions for IBD.

Conclusion

Nutritional interventions clearly have great potential to reduce disease activity and maintain remission in IBDs. Diet is known to be a contributory factor to IBD development, and alterations in diet can modify the disease course. Adjuvant nutritional therapies could be used with conventional care or considered as alternative treatments in cases of drug intolerance or treatment resistance. Specific dietary approaches and nutritional interventions have some, albeit limited, clinical evidence to suggest they can modify gene expression, have anti-inflammatory effects, induce mucosal healing, normalise intestinal microbiota, reduce disease activity and/or help maintain remission. A pragmatic integrative model for the personalisation of nutritional therapy in patients with active or latent IBD, incorporating disease-modifying dietary recommendations and nutrient-based supplements holds promise, and deserves further investigation and research.

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Butyrate Therapy for Treatment-Resistant Ulcerative Colitis: A Case Study

Beverly Gibbs and Benjamin I. Brown

Abstract

A number of patients with ulcerative colitis (UC) fail to achieve clinical remission with standard treatments, and may become less responsive to these treatments over time. Butyrate, a short-chain fatty acid, plays a major role in the immune homeostasis of the colonic mucosa, and oral butyrate has shown some promise as an adjuvant therapy in a small number of clinical studies, including for treatment-resistant patients. This case report describes an individual with a diagnosis of UC resistant to pharmacological and nutritional interventions who responded well to a trial of oral butyrate. Butyrate appears to be a promising therapy for UC, but questions around its efficacy, personalisation and safety require further investigation.

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Introduction

Inflammatory bowel diseases (IBDs), including ulcerative colitis (UC), have a high prevalence in developed countries.[1] In the UK, the prevalence of UC is approximately 243 per 100 000, equivalent to 146 000 people living with UC.[2] The treatment of IBDs is primarily based on pharmacological interventions, in particular aminosalicylates, corticosteroids, immunomodulators, immunosuppressants and biologics; however, a significant number of patients fail to achieve clinical remission and may become less responsive to these treatments over time.[3] For example, sulfasalazine and 5-aminosalicylates have an expected remission rate of about 50%.[4] And, independent of treatment response, 90% of people with UC will experience a relapsing course of their illness.[5] More effective and safer management approaches are needed and may be aided by improved understanding of the disease pathophysiology.[6] One possible approach is the personalisation of a wider range of candidate therapies, not only pharmacological interventions, based on an individual's unique environmental exposures and phenotypic expression.[7]

Ulcerative colitis is a chronic inflammatory disease characterised by mucosal inflammation that is thought to be the result of several contributing factors, including genetic susceptibility, a dysregulated immune response, altered gut microbiota and various environmental factors.[8] Although UC is a heterogenous disease, one possible disease pathway that transverses environmental, genetic, microbial and immunological influences is altered butyrate utilisation.[9] Butyrate is a short-chain fatty acid (SCFA), mainly produced by the fermentation of dietary fibres by butyrate-producing bacteria, and plays a major role in the physiology and immune homeostasis of the colonic mucosa.[10]

Butyrate production and metabolism may be impaired in patients with UC. Production of butyrate may be reduced due to a low-fibre diet,[11] although it has been observed that there are large individual differences in butyrate synthesis in response to fibre, likely due to the intrinsic butyrate-producing capacity of a person's resident bacteria.[12] Indeed, patients with UC have generally been found to have low levels of butyrate-synthesising bacterial species such as *Roseburia* and *Faecalibacterium prausnitzii*.[13] Also, stool samples of patients with IBDs have generally found low levels of butyrate when compared with healthy controls.[14,15,16,17]

Metabolism of butyrate may be impaired in the colonocytes of patients with IBD, with reduced butyrate transport limiting uptake and resulting in cellular butyrate deficiency.[18] This metabolic issue suggests that dietary fibre and butyrate-synthesising bacteria may not always be related to low butyrate levels. In support of this, a study in patients with active IBD found that decreased butyrate concentrations were not related to lower stool content of butyrate-producing bacteria.[19]

Butyrate supplementation has been explored as a management approach in IBDs, and would be of particular interest if it can overcome poor response to increased dietary fibre intake, low stool content of butyrate-producing bacteria, and/or impaired butyrate transport and metabolism, discussed above. Treatment with oral butyrate salts in combination with mesalazine has yielded promising results. Patients (n = 12) with UC who received butyrate (4 g/day) plus mesalazine for 6 weeks reduced disease histology and symptoms scores better than mesalazine alone.[20] In another report, patients with UC (n = 216) with a poor response to mesalazine had a marked improvement of symptoms and in the endoscopic appearance of mucosa with the addition of 921 mg butyrate and 750 mg inulin.[21] Also, butyrate with inulin plus mesalazine in active UC (n = 37) resulted in an 85% response rate compared with 55% with mesalazine alone.[22] The butyrate and inulin group also had improved capacity for butyrate synthesis by the gut microbiota, and lowered serum inflammatory biomarkers.[20]

A potential mechanism of action of butyrate was explored in a clinical trial of patients with IBD. In this study, oral butyrate (1800 mg/day) or placebo was administered with conventional therapy for 2 months, and clinical disease activity, quality of life and faecal microbiota from stool samples were assessed by 16S sequencing. Oral butyrate increased SCFA-producing bacteria in patients with UC (*Lachnospiraceae* spp.) and the butyrate-producing bacteria in patients with Crohn's disease (*Butyricicoccus*).[23] However, no change in disease activity was observed in this study.

The evidence suggests that some patients with IBD could have a significant clinical response to oral butyrate therapy. The following case report describes an individual with a diagnosis of UC resistant to pharmacological and nutritional interventions who responded well to a trial of oral butyrate under the care of a Nutritional Therapist. In the UK, Nutritional Therapy is an evidence-based practice that utilises dietary therapies, nutrient-based supplements and lifestyle medicine to improve underlying pathophysiology in an integrative, personalised and patient-centred model of care.[24]

Case presentation

Presenting concerns

The case was a 62-year-old male, non-smoker, with a 25-year history of UC. His primary complaint was frequent, loose bowel movements, with urgency and incomplete evacuation.

Case history

For a number of years following diagnosis, remission had been obtained through aminosalicylate treatment (Mezavant) with flare-ups occurring approximately annually, treated with corticosteroids at doses of up to 50 mg/day. The case was seen regularly at an IBD clinic, under the care of a consultant gastroenterologist.

In recent years, flare-ups had increased in frequency to approximately every 6 months, and then more recently (since 2019) to every 3 months. Each time, oral steroids were prescribed to reduce symptoms, with aminosalicylate treatment for maintenance and prednisolone steroid enemas at the first sign of a recurrence (with the aim of minimising systemic steroids).

In 2012, immunomodulator therapy was trialled (azathioprine and mercaptopurine), but this was poorly tolerated, with the case reporting severe nausea, lethargy and low white cell count. In the same year, the case suffered a herpes zoster (shingles) infection, resulting in 6 weeks absence from work. UC treatment then reverted to maximum doses of Mezavant and oral steroids as required.

Various dietary interventions were tried in this period, including gluten-free (dietary gluten avoidance), dairy-free (dietary dairy avoidance), specific carbohydrate diet (a restrictive, grain-free diet plan developed for the management of IBD) and low-FODMAP diet (an elimination diet used to help manage the symptoms of irritable bowel syndrome). Small amounts of benefit were obtained with each (e.g. more energy, slightly reduced frequency and urgency), but none gave sustained relief of symptoms. Supplementation with various probiotics over this period (e.g. VSL#3) and prebiotics also appeared to give no relief.

The case undertook regular monitoring by an NHS IBD clinic, and was assessed by endoscopy and biopsy at intervals.

Side-effects suffered from corticosteroids

In the meantime, the case was diagnosed with corticosteroid-induced osteoporosis in the spine and was prescribed AdCal (combination calcium and vitamin D). Weekly bisphosphonates (alendronic acid) were also commenced at 70 mg.

In July 2015 the case was hospitalised for an unresponsive disease flare-up that had resulted in a 10 kg weight loss. The case

was treated with very-high-dose steroids intravenously for 24 hours, being discharged to continue oral treatment the next day. Following this experience, the case decided to limit working hours to part-time because of reduced quality of life.

The option of surgery was discussed in 2018, but the decision was made to defer this as the last possible resort.

In March 2019, the case suffered a 5-mm calcium oxalate kidney stone, which was passed naturally (but with severe pain) in July 2019 without further treatment. He was then advised to stop taking AdCal by his physician as this could have been the cause.

In May 2020, the case experienced the start of the latest flare-up, following a short period of remission of 3 months. Sleep was disturbed in this period also. His physician decided to manage this conservatively with additional steroid enemas daily due to the osteoporotic side-effects of oral treatment, but only partial relief was obtained.

Unresponsive to treatment

In June 2020, the case, still on Mezavant, was prescribed oral corticosteroids once more, but this did not resolve symptoms.

In August 2020, funding was obtained by the IBD clinic for treatment with the biologic tumour necrosis factor (TNF)-alpha inhibitor Imraldi (40 mg once every 2 weeks), administered by self-injection. After some promising indications of possible relief, the case became unresponsive within weeks, and a sigmoidoscopy in November 2020 confirmed the following symptoms:

- redness in the distal colon;
- loss of vascular pattern;
- patchy erosions.

Faecal calprotectin at this time was 322 µg/g (ideal level < 100 µg/g) despite steroid treatment (Table 1). A more frequent dose of Imraldi (40 mg once a week) was tried at this point, but without success.

In December 2020, the IBD clinic advised the next stage of treatment would be vedolizumab, a 'gut-selective integrin blocker' that targets white blood cells, delivered by intravenous infusion, for which funding approval would be sought. The suggested response rate of this medication was 40–45%.

Intervention

Before this latest treatment commenced, the case's Nutritional Therapist became aware of the potential use of butyrate supplementation for symptomatic relief of UC.

The case commenced oral calcium magnesium butyrate at a dose of 1.2 g per day, whilst continuing Mezavant treatment at 4.8 g/day.

Within 2 days, the case felt a positive response to butyrate, and within 4 days the frequency of bowel movements had reduced from eight–11 per day to four–six per day, with less urgency.

Eleven days later, the butyrate dose was increased to 2.4 g per day (in two divided doses) and there was further improvement to two–four bowel movements per day, with normal stool and feeling of complete evacuation.

From January 2021 to the present day, stool frequency has stabilised at two–three per day (Figure 1) with no feelings of urgency (Figure 2). The case reports that bowel function feels much better, even compared with the effects of previous symptom alleviation from corticosteroids. Faecal calprotectin is reported to have reduced to 242 µg/g.

Figure 1: Number of bowel movements per day (1–12).

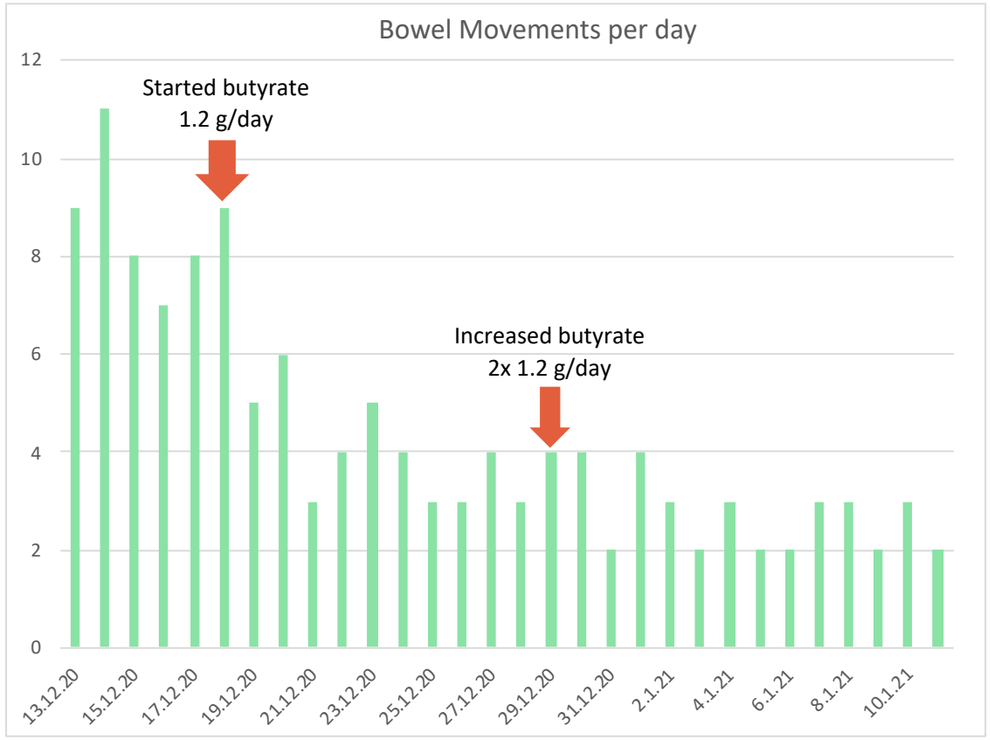
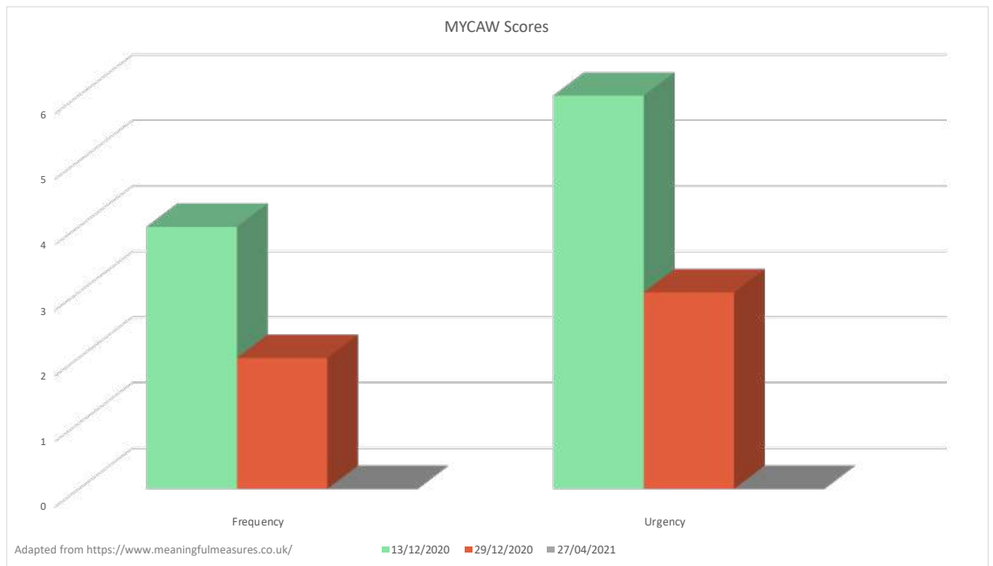


Figure 2: Improvement in symptom scores.



Self-reported MYCAW scores prior to treatment (13/12/3020) to post-treatment (29/12/20) and present day (27/04/21). MYCAW is an individualised questionnaire designed for evaluating holistic and personalised approaches to supporting people.[25]

Progress to date

The case reports continued relief of symptoms from combined Mezavant and butyrate. The butyrate supplement is well tolerated and no side-effects have been reported; the pungent smell from butyric acid is not a deterrent to this case and does not linger on the breath.

The case has been able to exercise at moderate–high intensity for 1–2 hours at a time on a regular basis, whereas previously the urgency for a bowel movement would have hampered this. Quality of life has returned, and the case is able to tolerate a wider variety of foods, maintaining a largely pescatarian, wholefoods diet.

An appointment with the consultant gastroenterologist in July 2021 to discuss the case's condition resulted in an agreement to continue oral butyrate as maintenance therapy. Body weight is stable at 73 kg (body mass index 23 kg/m^2).

Table 1: Faecal calprotectin test results

Date	Value	Range (NHS): Ideal: < 100 µg/g; Borderline/intermediate: 100–250 µg/g; Urgent referral: > 250 µg/g
19/04/2021	242 µg/g	
13/11/2020	322 µg/g	

Discussion

Butyrate represents an emerging novel therapy for UC that could be used in a personalised way for cases who have a poor response to standard management approaches, including pharmacotherapy, probiotics, prebiotics and dietary therapy, as supported by a small number of exploratory studies,[18,19,20] and the case described here. Important but unanswered questions remain that could help clarify the role and use of butyrate. Firstly, could biomarkers be used to predict candidates for therapy? Butyrate-synthesising bacterial species and butyrate can be assessed clinically with stool analysis, but it is currently unknown if they can be used to predict treatment response. The high level of individual variability in microbial markers and metabolism could mean that such biomarkers may not be reliable. Microbiome testing is fraught with important limitations that impair translation to clinical practice, including the high variability and instability of an individual's microbiome, unpredictable response to nutritional interventions, and important variations in laboratory methods and results, all of which impact reliability and usefulness of test data.[26] Similarly, assessment of butyrate in stool samples is limited by significant individual variability, variation from day to day, and the time of day of the sample.[27]

Secondly, what is the optimal dose of butyrate? Currently there are few clinical studies and no dose–response studies to inform dose regimes. It is plausible that doses higher than those used to date (up to 4 g/day in UC) would be more effective and have relevance for active UC. One analysis suggests that, based on daily butyrate production and requirements, higher doses (up to 10 g/day) may be optimal.[28] Dosage regimes need further exploration, including the assessment of higher doses for active disease, and the optimal dose regimes for supporting maintenance of remission.

Thirdly, it would be interesting to understand the potential for butyrate as a monotherapy. Clinical research to date suggests it may be better suited to use as an adjuvant to pharmacotherapy, and possibly prebiotics, probiotics and nutritional interventions, but its use as a monotherapy has not yet been explored in UC, and given butyrate's potential safety it may be an interesting candidate for maintaining IBD remission.[29] This case report suggests it may be useful for maintaining UC in remission, but this requires validation with further study.

Finally, although butyrate is generally considered very safe and well tolerated, rigorous safety assessment is warranted if butyrate is to have more widespread use.[30]

Evidence to date does suggest a high degree of safety with no toxicity, side-effects, nutrient–drug interactions or safety concerns from human clinical trials in patients with IBD and other gastrointestinal disorders, but this requires more rigorous assessment.[28]

Conclusion

This case report suggests a novel role for oral butyrate therapy. In a case of UC that was resistant to conventional therapy and nutritional interventions, butyrate administration appeared to result in significant control of symptoms and maintenance of remission. It is hypothesised that this may be due to exogenous butyrate supporting an individual's higher metabolic demand for endogenous butyrate that could not be met due to impaired butyrate synthesis and/or increased metabolic requirement, although this theory requires validation with more research. Evidence to date suggests that butyrate may be a useful, safe therapy that could complement the usual care of IBD.

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Case Report
Butyrate Therapy for Treatment-Resistant Ulcerative Colitis: A Case Study

Ashwagandha: A Review of Clinical Use and Efficacy

Karin Elgar

Abstract

Ashwagandha has a long tradition of use in Ayurvedic medicine, and is best known as an adaptogen, a compound that can help increase our resistance to stress. Preclinical research has also shown ashwagandha to have anti-inflammatory, antimicrobial, antioxidant, antidiabetic, anti-tumour, anti-ageing and neuroprotective properties. Steroidal alkaloids and lactones, including withaferin A and withanolides, are thought to be some of the most active compounds of the herb. Clinical research in humans has shown ashwagandha to be safe and of benefit in a range of conditions, including stress/anxiety, athletic performance, cognition, diabetes, insomnia and male infertility. Ashwagandha is generally considered to be safe, with a few minor possible side-effects, although care should be taken alongside certain drugs.

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Introduction

Ashwagandha (Withania somnifera), also known as Indian ginseng or winter berry, has been used in Ayurvedic medicine for more than 3000 years. It belongs to the Solanaceae (nightshade) family of plants, and grows wild in Africa, the Mediterranean and India. Ashwagandha is also cultivated for medicinal purposes.[1]

Although the berries and leaves appear to have some medicinal effects, it is mostly the roots that have been used traditionally and have been subject to modern medical research. The active constituents include steroidal alkaloids and lactones, including withaferin A and withanolides.[2]

In Ayurveda, ashwagandha has been used for a wide range of indications, including as a liver tonic, an anti-inflammatory, an astringent, an aphrodisiac and an adaptogen, for conditions such as insomnia, bronchitis, asthma, ulcers, emaciation and dementia. Modern preclinical research has confirmed anti-inflammatory, antimicrobial, antioxidant, anti-stress, antidiabetic, anti-tumour, anti-ageing and neuroprotective properties.[1,3]

Clinical uses

Anxiety/stress

Ashwagandha is considered to be an adaptogen, that is a compound that can modify our stress response in order to increase our resistance to stress.[4] Ashwagandha is probably most revered for these adaptogenic properties, and its benefits in terms of reducing stress and anxiety have been extensively studied in both preclinical and clinical studies.

A number of double-blind, placebo-controlled trials have shown that ashwagandha can reduce anxiety scores by up to 70% or more in patients with anxiety disorders[5,6,7] or high stress levels.[8,9,10,11] Dosages in these studies ranged from 125 to 2000 mg per day of ashwagandha extract. Significant improvements in anxiety and depression have also been seen with ashwagandha extracts, 1000 mg per day, in patients with schizophrenia, where positive outcomes were also observed in other disease parameters.[12,13]

A small double-blind, placebo-controlled trial also showed significant improvements in patients with obsessive compulsive disorder (OCD) who took ashwagandha extract, 120 mg per day, in addition to selective serotonin reuptake inhibitors (SSRIs), with a decrease in OCD severity from 26 to 18 (on a scale of 0–40), independent of whether patients suffered from concomitant anxiety disorders.[14]

Dosages as well as strengths of the extracts have varied in the above studies. A number of studies in people with high stress levels have shown a dose-dependent increase in efficacy, and levels of 300 mg twice a day have given the most benefits while also being safe.[8,10,11] Most studies had a duration of 2 months, with beneficial effects being observed as early as within 2 weeks of intervention.[5] Benefits usually increased over 6–10 weeks. Most studies used extracts of the root only, although some used extracts of both root and leaves.[11]

A number of mechanisms appear to contribute to the adaptogenic and anxiolytic properties of ashwagandha. Preclinical research has shown that ashwagandha extracts have γ-aminobutyric acid (GABA) ergic action, although neither withaferin A nor withanolide A appear to be responsible for this action.[15]

Clinical trials have shown that ashwagandha works by exerting a balancing effect on the hypothalamus–pituitary–adrenal (HPA) axis, lowering cortisol levels in stressed adults by 23–33%.[9,10,11,16]

It has also been suggested that withanolides are hormone precursors and that ashwagandha acts as an amphoteric, that is it can bind to hormone receptors and exert a mild effect where hormone levels are low, while blocking the receptor when hormone levels are too high.[1]

Athletic performance

As an adaptogen, ashwagandha has been popular for increasing stamina and athletic performance, a use that is backed up by several clinical studies.

Ashwagandha extracts have been shown to increase athletic performance in both the general healthy adult population[17,18,19] and professional/elite athletes.[20,21] VO_2 max, a measure of cardiovascular fitness, has been shown to increase by 6–14% over study periods of 4–12 weeks.[17,18,19,20,21] Ashwagandha extracts have also been found to increase muscle mass and strength, and improve muscle recovery.[22,23]

Quality of life scores (including physical health, psychological health, social relationships and environmental factors) have also been reported to improve significantly more with ashwagandha than with placebo in athletic adults,[18] although another trial found no difference in exercise-related emotional/mental factors.[22]

Dosages used have been in the range of 330–1000 mg per day. Apart from one study that used an extract from roots and leaves,[22] all of the above trials used root extracts. Benefits have been seen after 4 weeks,[17] although most trials ran for 8 or 12 weeks.

Several mechanisms have been discussed to explain the results seen in athletic performance. The ability of ashwagandha to increase testosterone in men and reduce cortisol would be expected to promote muscle development, while its antioxidant and anti-inflammatory properties may support muscle recovery. Ashwagandha appears to support mitochondrial function and as such energy levels, while its adaptogenic effects on the nervous system may also have benefits in terms of athletic performance.[18,23] Increases in haemoglobin have been seen in clinical trials, which may contribute to increased athletic performance.[20]

Cognitive function/memory

Ashwagandha has shown favourable results with regards to cognitive function and neuroprotection in preclinical research. While animal research looks promising in a number of conditions, including Alzheimer's disease and Parkinson's disease, human trials in this area to date are limited to cognitive function.[24]

Significant benefits in terms of cognitive function and psychomotor performance have been observed in a number of different patient populations, including healthy men,[25] people with mild cognitive impairment[26] and bipolar disorder.[27]

Dosages have been in the range of 300–500 mg of ashwagandha extract (twice a day). While one study used an extract of the root only,[26] two other studies used extracts of root and leaves.[25,27] In healthy men, significant improvements were seen in as little as 2 weeks; in other studies, benefits increased over the 8-week study periods.

A number of possible mechanisms have been discussed in the literature. Neuroinflammation plays an important role in the development of neurodegenerative disorders, so the anti-inflammatory properties of ashwagandha are likely to contribute. Ashwagandha has also been found to increase brain-derived neurotrophic factor, thus protecting brain cells and promoting neuroplasticity.[28] Ashwagandha also modulates oxidative stress markers in the brain, including levels of superoxide dismutase, catalase, lipid peroxidation and glutathione.[24]

Diabetes

Ashwagandha has shown beneficial effects on blood glucose, fasting glucose and HbA1c in animal models; however, there is limited evidence from randomised-controlled clinical trials for its use in diabetes.[29]

In a double-blind, placebo-controlled trial of ashwagandha extract, 1200 mg per day for 30 days, levels of fasting blood glucose and serum triglycerides significantly improved in patients with schizophrenia and metabolic syndrome, while no improvements were seen in the placebo group.[30]

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Improvements in glycaemic control have also been seen in two other studies,[31,32] although these were small, open-label trials, and in one of them patients were also given dietary and lifestyle advice.[31]

Two further studies showed benefits in endothelial function, lipid profile and oxidative stress in patients with type 2 diabetes that was well controlled with metformin. One study[33] compared 250 mg twice a day and 500 mg twice a day of an ashwagandha root extract versus placebo for 12 weeks; the other[34] compared 500 mg twice a day of an ashwagandha root and leaves extract versus another herb, versus a combination of the two herbs for 12 weeks. Significant improvements over placebo were seen with 500 mg of ashwagandha extract per day, but were significantly greater with 1000 mg per day. Increases of 31% and 43% in glutathione, respectively, were observed in the two studies.

Three of the above studies used dosages higher than generally given for other indications: 1000–1200 mg of extracts and 3000 mg of root powder per day,[30,33,34] although beneficial effects were also seen with lower dosages: 500–600 mg of extract per day.[31,33] One study compared 500 mg with 1000 mg per day, and found benefits to be better with the higher dose.[33] Durations of treatments ranged from 1 to 3 months, with improvements noted after 1 month.[30,32]

In vitro studies suggest that the antidiabetic actions of ashwagandha are mediated through an increase in cellular glucose uptake in both skeletal and fat cells, and an increase in insulin secretion. While both leaf and root extract produce the former mechanism, the latter only occurs with leaf extracts. The main active compound responsible for these actions appears to be withaferin A.[35] The antioxidant potential of ashwagandha has been shown in healthy volunteers[36] and confirmed in some of the above studies, and may contribute to the positive effects seen in type 2 diabetics. Due to the fact that stress, and elevations in cortisol levels, can have a negative effect on blood glucose control, the antidiabetic effects of ashwagandha may also be mediated in part through its balancing effect on the HPA axis.[31]

Insomnia/sleep

The Latin name of ashwagandha, Withania somnifera, alludes to its sleep-promoting properties, 'somni-fera' meaning 'sleep-inducing'. The herb is thought to 'rejuvenate the nervous system', easing stress and thus promoting sleep without being sedating.[37]

Over the past few years, five double-blind, placebo-controlled trials have confirmed the sleep-promoting effects of ashwagandha in healthy adults,[38] stressed healthy adults,[10] adults with anxiety and insomnia,[6] adults with insomnia,[38] healthy subjects scoring high on non-restorative sleep,[39] and healthy elderly people.[40]

Various outcome measures were used in these studies, including actigraphy (collection of sleep parameter measures using a watch-like device) and sleep questionnaires, with improvements observed using both. Improvements in sleep quality were in the range of 30–72%, with improvements generally higher in people with sleep problems.[38]

Most studies used an ashwagandha root extract, 600 mg per day, while one study used an extract of both roots and leaves, 120 mg per day.[39] The latter gave the biggest improvements in sleep quality as assessed by questionnaire – 72%. The duration of treatments ranged from 6 to 12 weeks, with gradual improvements over the study periods where outcomes were measured at different time points.[6,40]

The stress-relieving properties of ashwagandha are likely to play an important role in improving sleep. Studies in animal models suggest that ashwagandha has GABAergic properties, which would also contribute to its benefits.[39]

Male fertility

The Sanskrit name ashwagandha means ‘smell of a horse’, and refers to the herb’s smell, as well as indicating that it transfers the virility and strength of a horse.[8] Although beneficial effects on male sexual function have not been confirmed in clinical trials (see below), five human studies have shown beneficial effects in male infertility.

Three of these were open-label studies that compared infertile men with normal sperm count and motility (normozoospermic), low sperm count (oligozoospermic) or low sperm motility (asthenozoospermic) with fertile controls. Infertile men were given an ashwagandha root powder, 5000 mg per day, for 3 months.[41,42,43,44] In one of these studies, sperm count increased by 363% in those with low sperm counts, while sperm motility increased by 149% in those with low sperm motility.[42] In another study, the partners of 14% of the initially infertile men got pregnant during the 3-month study period.[41]

These studies also looked into a number of parameters to establish possible mechanisms. They found that ashwagandha increased testosterone and luteinising hormone (LH), while decreasing follicle-stimulating hormone (FSH)[41,42,44] and also decreasing cortisol levels in stressed men.[41] The potential of ashwagandha to support a healthy HPA axis, normalising cortisol levels and raising testosterone levels in stressed men has been confirmed in other studies.[9]

The above studies also showed that, compared with healthy fertile men, sperm of the men in the infertile groups had higher levels of oxidative stress and apoptotic cells, and lower levels of antioxidants, which improved with ashwagandha supplementation.[43] This suggests that the antioxidant and possibly nutritional properties of ashwagandha may also contribute to the observed improvements in fertility.

Two more recent double-blind studies have confirmed these results. One found that the same ashwagandha regimen as in the above studies was as effective as the infertility drug pentoxifylline in improving sperm count, motility and morphology.[45] The other study used an ashwagandha root extract, 675 mg per day for 3 months, which led to significant increases in sperm concentration, semen volume and sperm motility by 168%, 53% and 57%, respectively, as well as a 17% increase in testosterone and a 34% increase in LH. All results were statistically significantly better than in the placebo group, which saw no improvements.[46]

Ageing

Based on its traditional use, ashwagandha has been suggested as an anti-ageing herb. However, although positive effects on cognitive function and increases in testosterone in men have been observed, further evidence to support the use of ashwagandha in this area is scarce.

One double-blind, placebo-controlled trial found a 15% increase in quality of life in elderly, generally healthy people with an ashwagandha root extract, 600 mg per day for 12 weeks, as well as improvements in sleep and mental alertness (see the section: ‘Insomnia/sleep’).[40] However, another study found no improvement in fatigue, vigour, sexual and psychological wellbeing in overweight men with mild fatigue, aged 40–70 years, with an extract of ashwagandha root and leaves, 600 mg per day for 8 weeks.[47]

Arthritis/joint pain

Considering the general popularity of ashwagandha and its known anti-inflammatory properties, there are surprisingly few studies published on its use in arthritis or other inflammatory conditions, other than neurological.

An open-label study of 77 patients with rheumatoid arthritis, published in 1999, found ashwagandha root powder, 3000 mg per day for 6 weeks, to be effective in relieving symptoms. Unfortunately, this study did not have a control group.[48]

Only one study, in 2016, investigated ashwagandha on its own in a double-blind, placebo-controlled design. Patients with knee pain received either 250 mg or 500 mg per day of an aqueous extract of ashwagandha root and leaves, or placebo, for 12 weeks. There was a gradual improvement in symptoms over the study period, with pain, stiffness and disability reduced by about a third at the end of the 12 weeks in the group receiving the higher dose, and by about 18–20% in the lower-dose group. These results were statistically significantly better than placebo.[49]

The authors of the above study attribute the analgesic activity of ashwagandha mostly to withaferin A, which has been shown to reduce the production of prostaglandins, mediating pain by inhibiting cyclo-oxygenase (COX). They also suggest that the soothing action of ashwagandha on the nervous system may contribute to the analgesic effects.[49]

Three further studies evaluated mixtures of various Ayurvedic herbs and minerals, which included ashwagandha, and found beneficial effects in osteoarthritis[50,51] and rheumatoid arthritis.[52]

Hypothyroidism

Increases in thyroxine levels with ashwagandha have been observed in mice, and so thyroid parameters were studied as part of a safety evaluation in a trial of ashwagandha on cognitive function involving 60 patients with bipolar disorder, where thyroid disorders are a common co-morbidity.[27] Researchers saw ‘abnormal’ thyroid results in 10 patients.[52,53] Three patients receiving ashwagandha extract had abnormal thyroid function tests at baseline, one with elevated thyroid-stimulating hormone (TSH), one with elevated T3 (possibly due to lithium treatment) and one with low T4. At the end of the study all three patients’ thyroid function tests had normalised, and all three had increases in T4 ranging from 7 to 24%. Of the seven patients on placebo who had abnormal thyroid function tests at baseline, six showed a reduction in T4, and only one showed an increase.[53]

In 2018, a double-blind, placebo-controlled trial of 50 patients with mild hypothyroidism (TSH 4.5–10 IU/l) confirmed a positive effect of an ashwagandha extract, 600 mg per day for 8 weeks, on thyroid function. Levels of TSH, T4 and T3 improved significantly after 4 weeks, and continued to improve further over the next 4 weeks, with final improvements of 17.4%, 19.6% and 41.5%, respectively. All results were significantly better than in the placebo group, which saw no significant improvements.[54]

The beneficial effect of ashwagandha on thyroid function may be mediated by its effect on the HPA axis, which in turn is inversely related to the hypothalamus–pituitary–thyroid (HPT) axis, in that chronically elevated cortisol can inhibit the HPT axis and lead to reductions in T4 and T3. The dopaminergic and anti-inflammatory properties of ashwagandha may also affect both the HPA and HPT axes.[54] Animal studies also suggest that ashwagandha may have a direct effect on thyroid activity and thyroid hormone metabolism.[55]

No further clinical trials have been published to date but, in view of such positive results and the clinical observation that thyroid dysfunction is often correlated with stress, ashwagandha appears to have potential therapeutic value for patients with subclinical hypothyroidism.

Sexual dysfunction, male and female

Ashwagandha is also often touted as an aphrodisiac, but scientific evidence is scarce in women and does not support this use in men. One double-blind, placebo-controlled pilot study found that an ashwagandha extract, 600 mg per day for 2 months, improved sexual function in otherwise healthy women with sexual dysfunction,[56] while a study in men with erectile dysfunction found no benefit of ashwagandha powder, 6000 mg per day for 2 months, over placebo on a number of measures and parameters.[57,58] A study in 40–70-year-old men with mild fatigue also found no improvement in sexual health despite increases in testosterone with an ashwagandha extract, 240 mg per day for 2 months.[47]

Safety

A review of 39 preclinical and 30 human trials,[2] including two in children, concluded that ashwagandha root extracts are safe and efficacious in a number of clinical applications. Preclinical safety and toxicity studies showed root extracts to be safe, with the only noted side-effects being mild depression of the central nervous system and an increase in thyroxine. No mutagenicity or genotoxicity was reported in preclinical experiments.

Human trials did not observe any serious side-effects or changes in vital signs, haematological and biochemical markers. A number of mild to moderate transient adverse events have been reported in clinical trials, including somnolence, giddiness, drowsiness, hallucinations, vertigo, nasal congestion (rhinitis), cough, cold, decreased appetite, nausea, epigastric pain/discomfort, gastritis, flatulence, loose stools, constipation, dry mouth, hyperactivity, nocturnal cramps, blurring of vision, hyperacidity, skin rash and weight gain.[2] However, where these were placebo-controlled studies there was no statistically significant difference in the number of adverse events between the ashwagandha and placebo groups,[8,13,45,54,59] except for somnolence, which was noted to be more common in the ashwagandha group (21%) than in the placebo group (9%) in a trial in patients with schizophrenia.[13]

A safety study in 18 healthy volunteers in 2012 evaluated increasing dosages of an ashwagandha extract (750 mg, 1000 mg and 1250 mg) for 10 days each. All but one volunteer tolerated the herb well at all dosages, and vital signs, blood glucose, uric acid, haematological and liver function tests remained in the normal range. Serum creatinine increased and blood urea nitrogen decreased on the highest dose, suggesting some negative effect on the kidneys. One volunteer experienced increased appetite and libido, and hallucinations with vertigo after 3 days on the lowest dose and had to withdraw from the study; the effects resolved on discontinuation of the herb.[60]

A case series from Iceland and the USA described five cases of liver toxicity attributed to ashwagandha supplements. Patients developed jaundice, and symptoms including nausea, lethargy, pruritis (itching) and abdominal discomfort within 2–12 weeks of starting the herb. None of them developed liver failure, and liver tests normalised within 1–5 months after stopping ashwagandha in four of the patients; the fifth was lost to follow-up. None of them took any hepatotoxic medication, although four of them also took other supplements.[61] The possible mechanism is unclear, and in clinical trials no elevations of liver enzymes or other hepatotoxicity have been observed. Contamination of herbs can occur, although this was ruled out in these cases.[62]

An investigation in 2011 looked into contamination of herbs with heavy metals and pesticides.[63] The authors found that samples of ashwagandha had levels of mercury and lead that were below maximum levels set by the World Health Organization, while arsenic and cadmium were below the detection threshold. The 28 pesticides that were tested for were also not detectable.

Cautions

Due to some of the therapeutic effects of ashwagandha, caution should be exercised in patients with certain conditions or on certain drugs, as there may be additive effects.[64] It should be noted that there are no reports of serious adverse interactions in the literature.

Diabetes

As ashwagandha may have antidiabetic effects, in theory ashwagandha may cause blood glucose levels to drop too low in diabetics on antidiabetic medication. Extra monitoring and adjustment of medication is recommended. A number of clinical trials used ashwagandha alongside oral antidiabetic medication and no untoward effects were noted.[31,33,34]

Hypothyroidism/hyperthyroidism

As ashwagandha can increase thyroid hormones, it should be used with caution/extra monitoring in people with hyperthyroidism or hypothyroidism and on hormone replacement (thyroxine) therapy to ensure thyroid hormones do not go too high.

Sedative medications, including benzodiazepines

Although ashwagandha is not considered to be sedative as such, sedation and depression of the central nervous system have been observed in humans and in animal models.[65] Concomitant use with sedative medications should therefore be avoided, to prevent excessive sedation. This effect should also be taken into account when anaesthesia is planned, and the herb should be stopped 2 weeks before surgeries.[64] In a clinical trial in patients with schizophrenia, ashwagandha was taken alongside antipsychotic and other medications. Although overall there was no difference in the occurrence of side-effects between the ashwagandha and placebo groups, somnolence was noted to be more common in the ashwagandha group (21%) than in the placebo group (9%).[13]

Blood pressure

Ashwagandha may lower blood pressure,[66] so patients on blood-pressure-lowering drugs or with low blood pressure should monitor their blood pressure more closely, and the dosage of any medication may need to be adjusted.

Autoimmunity

Ashwagandha may increase the function of the immune system, and as such interfere with immunosuppressant drugs; it should be used with care in patients with autoimmune conditions.[64]

Pregnancy and breastfeeding

The seeds of ashwagandha have traditionally been used in parts of India to enhance lactation; however, there is no information from clinical trials regarding the safety of ashwagandha during breastfeeding, and it should therefore be avoided.[67]

Ashwagandha may lead to miscarriage, and so should be avoided during pregnancy or when pregnancy is planned.[64]

Age limits/minimum age

Ashwagandha has traditionally been used as a tonic and growth promotor for malnourished children.

Two studies2 have investigated the use of ashwagandha in children: one uncontrolled open-label study in 8–12 year olds with mild nutritional deficiencies; and one double-blind, placebo-controlled trial in healthy 8–12 year olds. In both studies, children took 2 g per day of an ashwagandha root powder for 60 days. Increases in body weight, haemoglobin and handgrip strength were seen in those children receiving the active herb, and no adverse effects were observed.

When root powders were used in studies in adults, dosages generally ranged from 3 to 5 g, so halving an adult dose for children aged 8–12 years appears to be an appropriate dose.

Another study compared two different traditional ashwagandha formulations, Ghrita (made with ghee) versus granules versus placebo in 111 children aged 3–12 years.[68] Aerobic capacity, body composition and muscular strength improved the most in the Ghrita formulation group, and the least in the placebo group. Children aged 3–7 years old received 2.5–4 g, and 8–12 year olds received 6–8 g daily for 6 weeks. The formulations and their strengths were not further described, and it is therefore difficult to extrapolate to pure root powders or extracts.

Conclusion

Human trials have confirmed the adaptogenic potential and clinical benefits of ashwagandha in a number of diverse conditions. The herb is generally safe in both adults and children, with only mild to moderate adverse effects reported during clinical trials. Care should be taken when ashwagandha is used alongside certain medications.

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Magnesium: A Review of Clinical Use and Efficacy

Karin Elgar

Abstract

Magnesium is a co-factor for more than 300 different enzymatic processes, and therefore plays a role in virtually every process in the cell, including cellular energy production, neuromuscular and cardiac function, maintaining ionic gradients, regulation of cell membrane receptors and DNA, RNA and protein synthesis. It is also an essential structural component for DNA and RNA on the cellular level, as well as in bones and teeth.

Whilst overt magnesium deficiency is rare, subclinical deficiency appears to be common, and increases the risk of many chronic conditions. Organic magnesium formulations, such as citrate, have been shown to be slightly better absorbed than inorganic ones, but many clinical trials have used inorganic formulations of magnesium, mostly oxide and chloride, and have shown benefits in a range of conditions, including cardiometabolic conditions, bone health, pain and constipation.

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Introduction

Magnesium is involved in hundreds of essential physiological processes, and adequate levels are therefore vital for general health. Whilst overt hypomagnesaemia appears to be relatively rare, suboptimal levels and inadequate dietary intakes are common, and may lead to an increased risk of chronic disease.

Magnesium deficiency can arise from poor diet, malabsorption, kidney disease, alcoholism and drug interactions. Various tests are in use to determine magnesium levels; however, none of them is considered particularly accurate. Serum levels are commonly used and, whilst low serum levels can accurately reflect magnesium deficiency, normal serum levels do not exclude low-grade magnesium deficiency. A combination of serum magnesium, urinary excretion and dietary intake measures appears to be the most practical and accurate way to determine magnesium status.

Good food sources include green leafy vegetables, cacao, wholegrains, nuts and seeds. Various dietary components, including certain types of fibre, phytates and oxalates can hinder absorption, which needs to be taken into account. In food supplements, organic formulations appear to be better absorbed than inorganic ones, and absorption is also better with several small as opposed to one large dose.

The most common side-effect of magnesium at high doses is diarrhoea. Caution is advised in patients with kidney disease as renal excretion plays an important part in magnesium homeostasis. Magnesium can also interact with a number of pharmaceutical drugs.

Functions

Magnesium is the fourth most abundant cation in our bodies (after sodium, potassium and calcium), and the second most common intracellular cation (after potassium).[1] Magnesium is a co-factor for more than 300 different enzymatic processes, and therefore plays a role in virtually every process in the cell.[2,3]

Magnesium is an essential co-factor for various enzymes involved in glycolysis and the Krebs cycle,[3] and mitochondrial magnesium also appears to play an important part in regulating mitochondrial function.[4] As such, magnesium is essential for cellular energy production.

Magnesium acts as an antagonist to calcium, for example in neuromuscular and cardiac function, and helps maintain ionic gradients, i.e. keeping intracellular sodium and calcium low and potassium high.[5] In the nervous system, magnesium is also involved in the regulation of various cell membrane receptors, including N-methyl-D-aspartate (NMDA) and y-aminobutyric acid (GABA) receptors.[3]

Magnesium is involved in DNA, RNA and protein synthesis, and is an essential component in DNA and RNA structure.[3] Magnesium also serves as a structural component in bones and teeth.

Deficiency

About 60% of magnesium is contained in the bones, another 30% in muscles. Less than 1% of total body magnesium is extracellular, i.e. in serum or plasma, and serum levels are maintained within a narrow range through homeostatic mechanisms, mainly renal excretion/reabsorption and gastrointestinal absorption of magnesium. When necessary, magnesium can also be released from bones and muscles to maintain serum levels when intake is low. Therefore, serum magnesium levels are not reflective of total body magnesium status, and normal serum levels do not necessarily rule out magnesium deficiency.[6]

A number of tests are used in research and in clinic to determine magnesium status; however, their accuracy and reliability is controversial,[6,7] which impacts on the interpretation and comparability of study results.

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- Retention of an intravenous (IV) magnesium load (administering IV magnesium followed by 24-hour urine collection) is considered the most reliable test, but is invasive and not practical for routine measurement. This test is also not reliable in individuals with impaired kidney function.
- Bone or muscle magnesium content through biopsy. Again, this is not practical for routine measurements.
- Urinary excretion.
- Red blood cell (RBC) magnesium. This test is often considered.
- The most commonly used test is serum magnesium levels; however, as mentioned above, this test is not reliable to identify mild magnesium deficiency as serum magnesium levels are tightly controlled and will therefore only drop in severe deficiency.
- Dietary intake of magnesium is commonly used to assess magnesium status. It is estimated that 30–50% of dietary magnesium is absorbed, but this depends on other nutrients. High intakes of fibre, phytates and oxalates can reduce magnesium absorption.[8]

Some authors suggest that a combination of serum magnesium, urinary excretion and dietary intake appears to be the most practical and accurate way to determine magnesium status.[7]

In clinical practice, RBC magnesium is commonly considered to be more accurate than serum level testing. Studies in animals support this method;[9] however, studies in humans are contradictory, with some finding RBC magnesium levels to be superior to serum levels in determining low magnesium status,[10] whilst others find it to be no more accurate.[11] When choosing tests in clinical practice, it is important to bear such contradictory findings in mind, and also to take into account dietary history and symptoms.

The definition of hypomagnesaemia (low serum levels of magnesium) varies according to the source, but is commonly described as serum magnesium levels of less than 0.7 mmol/l[12] although, more recently, BMJ Best Practice considered levels of below 0.9 mmol/l to constitute hypomagnesaemia.[13] It is generally agreed that hypomagnesaemia is indicative of low total body magnesium levels, but that serum levels can remain stable despite low total body magnesium stores due to the various regulatory mechanisms described above.

Acute symptoms of hypomagnesaemia do not usually become apparent until serum levels drop below 0.5 mmol/l.[14] As hypomagnesaemia is commonly associated with other metabolic abnormalities, in particular, hypokalaemia, hypocalcaemia and metabolic acidosis, it is difficult to determine which symptoms are solely due to the hypomagnesaemia.[15] Anorexia, nausea, vomiting, lethargy and weakness are typical early symptoms of magnesium deficiency.[15] Symptoms can be grouped into the following.

- Neuromuscular:
  - Muscular weakness, apathy, tremors, paraesthesia, tetany, vertical nystagmus and positive Chvostek's and Trousseau's signs.
  - Seizures, drowsiness, confusion and coma occur at magnesium concentrations below 0.4 mmol/l.
- Cardiovascular:
  - Various electrocardiogram changes.
  - Atrial and ventricular arrhythmias.
- Metabolic:
  - Hypokalaemia, hypocalcaemia, metabolic acidosis.

Whilst overt magnesium deficiency is rare, magnesium insufficiency appears to be common and may have significant implications for long-term health. Longer-term complications

of magnesium deficiency that commonly go unrecognised include the following.[2,14]

- Altered glucose metabolism;
- Metabolic syndrome;
- Hypertension;
- Atherosclerosis;
- Osteoporosis;
- Asthma;
- Migraines;
- Pre-eclampsia;
- Cardiovascular disease (CVD).

These will be discussed in detail below in **Clinical uses.**

Possible causes of hypomagnesaemia include the following.[15]

- Low dietary intake:
  - – Malnutrition, including anorexia nervosa.
- Malabsorption:
  - – Coeliac disease;
  - – Inflammatory bowel disease;
  - – Chronic diarrhoea;
  - – Steatorrhoea;
  - – Short bowel syndrome.
- Parathyroid disorders.
- Chronic alcoholism.
- Various medications, including:
  - – Proton pump inhibitors (PPIs);[16]
  - – Diuretics, including loop and thiazide diuretics;
  - – Some antimicrobials, including Amphotericin B, aminoglycosides, Foscarnet;
  - – Chemotherapy drugs, such as Cisplatin;
  - – Immunosuppressants, such as Tacrolimus, cyclosporine.

Prevalence estimates for hypomagnesaemia are thought to be in the range of 2.5–15% of the general population, but as it is often asymptomatic it may be commonly underdiagnosed.[17] The largest prevalence study, conducted with over 16,000 unselected subjects in Germany, found a prevalence of 14.5%.[18] Interestingly, the authors used a definition of hypomagnesaemia of < 0.76 mmol/l, and noted that prevalence would only be 2% if they used a more conservative cut-off point of < 0.7 mmol/l. Prevalence appears to be significantly higher in specific populations: 65% of patients in intensive care units; and 30% in a study on subjects admitted for alcoholism.[17]

Food Sources

Magnesium is part of the chlorophyll molecule in plants, which is what gives plants their green colour. Green leafy vegetables are therefore one of the best sources of dietary magnesium. Nuts and seeds, pulses and wholegrains are other good sources, although these foods are also high in phytates, which hinder magnesium absorption. Refined and highly processed foods tend to be depleted of magnesium.

Table 1: Best food sources of magnesium[19]

	mg per 100 g	mg per serving (serving size)
Spinach, cooked	87	157 (1 cup/180 g)
Swiss Chard, cooked	86	150 (1 cup/130 g)
Kale, cooked	25	30 (1 cup/ 118 g)
Quinoa, cooked	64	118 (1 cup/185 g)
Wholewheat spaghetti, cooked	54	76 (1 cup/140 g)
Brown rice, cooked	39	76 (1 cup/195 g)
White beans, cooked	63	110 (1 cup/175 g)
Red kidney beans, cooked	45	77 (1 cup/172 g)
Pumpkin seeds	592	168 (1 oz/28 g)
Cocoa powder	499	27 (1 tbsp/5 g)
Brazil nuts	376	105 (1 oz/28 g)
Almonds	272	77 (1 oz/28 g)
Dark chocolate	228	65 (1 oz/28 g)

The recommended magnesium intake varies from country to country, and is also dependent on age and sex (Table 2).[20,21] Dietary surveys in both the UK and USA suggest that a high proportion of individuals are not getting the recommended intake through diet.

- US National Health and Nutrition Examination Survey (NHANES) 2013–2016: average intake for adult men was 344 mg magnesium per day, and for women 270 mg, with 55% and 51% of adult men and women, respectively, not getting the recommended intake from food (fortified and non-fortified) and water alone.[22]
- UK National Diet and Nutrition Survey (NDNS): average intake of magnesium from food was 302 mg for men aged 19–65 years, and 238 mg for women in this age group, which is below the reference nutrient intake (RNI)[a] for women. Fourteen percent of men and 11% of women were getting less than the lower reference nutrient intake (LRNI), which is 190 mg for men and 150 mg for women. The average intake in those aged over 65 years was 242 mg, with 16% having a magnesium intake of less than the LRNI.[23]

Table 2: UK RNI and US recommended daily allowance (RDA) for magnesium

UK RNI	
Men 19–49 years	300 mg
Women 19–49 years	270 mg
Men 50+ years	300 mg
Women 50+ years	270 mg

RNI, reference nutrient intake.

US RDA	
Men 19–30 years	400 mg
Men 31–50 years	420 mg
Men 51+ years	420 mg
Women 19–30 years	310 mg
Women 31–50 years	320 mg
Women 51+ years	320 mg

RDA, recommended daily allowance.

Supplements

Magnesium is mostly absorbed via both saturable and non-saturable active transport pathways in the small intestine; smaller amounts are absorbed in the colon. Magnesium is absorbed as Mg2+ ions. Absorption rates depend on the magnesium status of the person, and are usually between 30% and 50%, but can be as high as 80% and as low as 20%.[24]

Due to serum magnesium levels being tightly controlled within a narrow range, absorption and bioavailability studies are fraught with methodological difficulties, which may explain the sometimes conflicting results. Overall, it appears that organic magnesium formulations are slightly better absorbed than inorganic ones.[24] In particular, a number of studies found magnesium citrate to be better absorbed than magnesium oxide.[25–27]

Despite these findings, many clinical trials have used inorganic formulations of magnesium, mostly oxide and chloride, and have shown benefits in a range of conditions (see below, **Clinical uses**).

Other factors play important roles in magnesium absorption, for example:

- Dietary factors:[28] high doses of other minerals, partly fermentable fibres (e.g. hemicellulose), non-fermentable fibres (e.g. cellulose, lignin), phytates and oxalates hinder, whilst protein, medium-chain-triglycerides, resistant starch, oligosaccharides, inulin, mannitol and lactulose enhance absorption.
- Magnesium dose:[29] several small doses are better absorbed than one large dose.

Transdermal magnesium has a long tradition of use, such as in Epsom salt (magnesium sulphate) and Dead Sea salt (which is high in magnesium) baths. However, good-quality evidence that magnesium is absorbed transdermally is lacking. A small safety study on a magnesium-containing barrier cream showed no significant increase in serum magnesium levels after 4 days of repeated administration.[30] A couple of small trials suggest that magnesium can be absorbed through the skin. A small pilot study suggests that a magnesium cream may increase serum magnesium levels over the course of 2 weeks.[31] Another small pilot study found that a magnesium chloride spray significantly increased magnesium levels in six out of nine subjects over 12 weeks by using hair mineral analysis to evaluate magnesium levels.[32] It should be noted that hair mineral analysis is not a generally recognised and standardised method of determining magnesium status, and that the evidence base for benefits of magnesium in clinical use (see **Clinical uses**) has been built on oral, and to a lesser extent IV, supplementation, rather than transdermal.

Clinical Uses

Metabolic syndrome

The term metabolic syndrome refers to a cluster of signs and symptoms, including insulin resistance, obesity, abnormal blood lipids and hypertension, which increase the risk of developing CVD and diabetes. The exact definition has changed over the years, and varies depending on the organisation.[33]

Epidemiological studies have shown consistently that metabolic syndrome is associated with low magnesium levels,[34–36] and that those with low intakes of magnesium are at increased risk of developing metabolic syndrome.[36–38]

A 2016 review of 27 double-blind clinical trials investigating the effects of supplementation with magnesium on components of metabolic syndrome (insulin resistance, hyperglycaemia, hypertension, dyslipidaemia) found that all six of the trials that looked at insulin resistance showed an improvement in the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR).[39] Results were mixed, with some studies showing improvements for hyperglycaemia, hypertension, triglycerides and low-density lipoprotein (LDL)-cholesterol, but others not.[39] The types of studies included in this review varied considerably with regards to study population, formulation and dose of magnesium, length of intervention and baseline magnesium levels.

Only one of the 27 studies included in the review mentioned above[39] investigated the effects of magnesium in patients with metabolic syndrome.[40] This double-blind, placebo-controlled trial found no significant improvements in any of the laboratory parameters tested in the magnesium (400 mg of magnesium chelate per day for 12 weeks) versus placebo group. Interestingly, 23% of participants were found to have hypomagnesaemia, and 36% had signs of cellular magnesium depletion at baseline, and magnesium status did not improve with supplementation.[40] The authors of this study hypothesise that insulin resistance, which was present in the majority of the patients, may have impaired magnesium entrance into the cells, and suggest that higher dosages may be necessary for patients with insulin resistance.

Two more recent double-blind, placebo-controlled studies in patients with metabolic syndrome and hypomagnesaemia at baseline found that magnesium supplementation improved not only magnesium status but also insulin sensitivity in both trials[41,42] as well as blood pressure (BP) and triglycerides in one of the trials.[42] The studies used magnesium oxide solution (385 mg elemental magnesium per day for 3 months)[41] and magnesium chloride solution (382 mg magnesium per day for 16 weeks),[42] respectively.

Another double-blind, placebo-controlled study in overweight, insulin-resistant but non-diabetic individuals with normal magnesium levels showed that 6 months of supplementation with magnesium aspartate hydrochloride, 365 mg per day, improved insulin sensitivity.[43]

The evidence overall supports the use of magnesium in patients with metabolic syndrome, in particular with regards to improving insulin sensitivity. Dosages used in clinical trials have ranged largely from 300 to 450 mg per day, and the most commonly used formulations were magnesium chloride, oxide and aspartate.

Type 2 diabetes mellitus

There has been a significant increase in T2DM over the past decades. In 2018, it was estimated that 13% of all US adults had diabetes, with 90–95% of these having T2DM,[44,45] whilst in the UK the prevalence of diabetes was estimated to be 7% in 2018/2019.[46] Both low dietary magnesium intake and low serum magnesium levels have been shown in epidemiological studies to increase the risk of developing T2DM,[47–51] as well as increase the risk of complications in those with T2DM due to poor glycaemic control.[52,53]

In 2017, a systematic review and meta-analysis of 28 randomised controlled trials (RCTs) including 1694 diabetic subjects found that magnesium supplementation improved a number of cardiovascular risk factors, including fasting glucose, high-density lipoprotein (HDL)- and LDL-cholesterol, triglycerides and diastolic BP. The authors noted that effects were more pronounced in patients with low magnesium levels.[54] For example, one RCT showed that 360 mg magnesium (as lactate) for 3 months did not change glycaemic control or blood lipids in diabetics with normal serum magnesium levels, 'normal' defined as > 0.74 mmol/l. It is noteworthy that mean serum magnesium levels at baseline were 0.92 mmol/l, which might be considered 'optimal'.[55]

A recent double-blind, placebo-controlled clinical trial showed that supplementing with 250 mg magnesium per day (as oxide) for 24 weeks improved glycaemic control, LDL- and total cholesterol, and carotid intima-media thickness, in diabetics receiving haemodialysis.[56] In another more recent randomised trial, 250 mg magnesium per day (as oxide, gluconate, lactate) improved glycaemic control in patients with T2DM after 3 months of supplementation.[57]

Magnesium has also been investigated as a supplement alongside other nutrients: 250 mg magnesium per day (as oxide) for 4 months as part of a comprehensive multivitamin and mineral supplement improved neuropathic symptoms, but not glycaemic control, capillary blood flow or electrophysiological measures in diabetics.[58] Concomitant supplementation of magnesium, 500 mg per day as oxide, and choline has been shown to improve inflammation, endothelial factors and coagulation biomarkers.[59,60] Meanwhile, supplementation with a honey fortified with magnesium, cinnamon and chromium led to a significant reduction in total and LDL-cholesterol, but no improvements in glycaemic control. The dose of magnesium in this trial was low: 120 mg per day (as citrate).[61]

The evidence shows that diabetics can benefit from magnesium supplementation in terms of improved glycaemic control and cardiovascular risk factors, especially in patients who are low in magnesium. Dosages used in studies showing benefits have generally ranged from 250 to 638 mg per day in a variety of formulations.

Hypertension

Magnesium is important for relaxation of the smooth muscles of the vascular system as well as other functions that are important in the regulation of BP.[6] Two meta-analyses of prospective cohort studies showed that BP was inversely related to magnesium levels and intake.[49,62] A number of cross-sectional studies also found an inverse relationship between magnesium intake and/or levels and BP,[63–68] although some cross-sectional studies do not confirm an association.[69]

A meta-analysis of 34 double-blind, placebo-controlled trials assessing the effectiveness of magnesium supplementation to lower BP in both subjects with and without hypertension showed a significant benefit of magnesium supplementation, and suggested that a dose of 300 mg elemental magnesium for 1 month was sufficient to increase serum magnesium levels and lower BP.[70] There was significant heterogeneity within the study results that may be explained by the theory that certain subsets of patients may benefit more than others. A meta-analysis of RCTs including only hypertensive patients with a systolic BP of > 155 mmHg and who had previously used antihypertensive drugs showed a particularly strong effect of magnesium supplementation, with a mean decrease in systolic BP of 18.7 mmHg and in diastolic BP of 10.9 mmHg.[71] A 2017 meta-analysis of 11 RCTs found that magnesium supplementation significantly lowered both systolic and diastolic BP in a subset of patients with prediabetes, insulin resistance or other chronic conditions.[72]

The evidence suggests a significant BP-lowering effect of magnesium, especially in those with hypertension or other chronic conditions, at a dose of 300 mg per day.

Cardiovascular disease

A 2013 meta-analysis of 19 prospective cohort studies concluded that both dietary magnesium intake and serum magnesium levels were inversely related to CVD risk, including coronary heart disease, death from CVD and stroke.[73] However, a more recent meta-analysis of 40 prospective cohort studies found a benefit of higher magnesium intakes only for heart failure and stroke, but not total CVD. It also found a lower risk of all-cause mortality in those with higher magnesium intakes.[74]

Atherosclerosis

Magnesium deficiency can cause calcification of soft tissues, and may promote the development and progression of atherosclerosis.[6] A number of epidemiological studies have shown an inverse relationship of atherosclerosis with serum magnesium levels[75–78] and dietary magnesium intake[79] in patients with both high and low cardiovascular risk.

A case series of 80 patients reports that a combination of injected and oral magnesium improved (non-vascular) soft tissue calcification in 75% of patients.[80] Also, a 6-month double-blind magnesium supplementation study showed that magnesium chelate, 600 mg per day, not only lowered BP, but also improved endothelial function and attenuated subclinical atherosclerosis in hypertensive women on magnesium-depleting anti-hypertensive medication.[81]

Although the evidence for benefits of magnesium in atherosclerosis is limited, the fact that magnesium also appears to improve many other cardiovascular risk factors suggests that recommending magnesium supplementation to patients with atherosclerosis seems warranted, at a dose dependent on other risk factors present.

Osteoporosis

Osteoporosis is characterised by a loss of bone mass that leads to a weakening of the bone and an increased risk of fractures. As mentioned above, magnesium forms a structural part of bones, and bones also serve as a reservoir for magnesium.[6]

Magnesium is intricately involved with vitamin D metabolism: magnesium is necessary for the synthesis and conversion of vitamin D, whilst vitamin D is also important for magnesium absorption.[82] Magnesium has been used to reverse vitamin D-resistant rickets.[83]

Epidemiological studies have shown lower bone mass density and an increased incidence of osteoporosis in people with low magnesium levels[84] and low magnesium intakes in both adults[85–87] and adolescents.[88] A meta-analysis of seven case–control studies including 1349 women showed that low magnesium levels are a risk factor for osteoporosis, although there were regional/racial differences.[89] Both high and low magnesium levels and intakes have shown harmful effects on bone health,[90] although the evidence is inconsistent.[91]

Evidence for the benefits of magnesium in bone health from supplementation studies is limited. Two short-term (30 days), open-label, controlled magnesium supplementation trials showed that magnesium decreased markers of bone turnover in healthy young men,[92] as well as in post-menopausal women.[93] The daily dosages were 365 mg (as carbonate and oxide) and 1830 mg magnesium citrate (it is not stated in the article whether this refers to elemental weight), respectively. A 12-month double-blind, placebo-controlled study on magnesium supplementation (300 mg as magnesium oxide) in children and adolescents with low magnesium intake showed an increase in bone mineral content.[94] An open-label, controlled trial of post-menopausal women with osteoporosis showed that magnesium supplementation (250–750 mg per day as magnesium hydroxide) for 2 years significantly improved bone density. Serum magnesium levels significantly increased during magnesium supplementation in this study.[95]

Based on the clinical evidence available, magnesium appears to be of benefit for bone health in children and adolescents as well as in healthy adults and post-menopausal women at a dosage of 300 mg per day in children and 250–750 mg per day in adults.

Asthma

Lower magnesium levels have been reported in asthmatics, but results from epidemiological studies are heterogenous. A recent metanalysis found an increased susceptibility for asthma with low magnesium levels only for Asians, whilst Caucasian and African population-pooled results did not show statistical significance.[96] There is evidence that in patients with asthma, the condition appears to be less well controlled in those with low magnesium levels,[97–99] although other studies did not find an association between magnesium levels and severity of asthma.[100,101] It is noteworthy that individuals in the latter two studies had magnesium levels within the normal range, whilst in the former studies asthmatics with worse pulmonary function/poorer control were considered to have magnesium levels below normal range, suggesting that asthmatics with low levels of magnesium are more likely to benefit from supplementation.

There is a reasonably large body of evidence for the use of IV magnesium sulphate in acute asthma attacks as an adjunct to other treatments, including bronchodilators and corticosteroids. The evidence is more consistent for children[102,103] than for adults.[104,105] Nebulised, inhaled magnesium sulphate has also been used in acute asthma exacerbations, alongside other treatments, but results from clinical trials are inconsistent, and systematic reviews and meta-analyses on the whole do not find enough evidence for significant benefits.[102,106,107]

A recent meta-analysis of seven RCTs evaluated the benefits of oral supplementation of magnesium in mild to moderate asthmatics. Whilst there were improvements in all outcome parameters, they were only statistically significant for one parameter, which led the authors to the conclusion that at present there is not enough evidence to recommend oral magnesium supplementation for asthmatics.[108] The authors point out that there was significant heterogeneity amongst the studies with regards to dose, formulation and length of treatment, and no sub-group analysis was performed to potentially identify those patients for whom magnesium supplementation may be of benefit. Looking at the studies individually, five out of the seven studies found a benefit of oral magnesium supplementation, possibly more so in those studies where magnesium levels were found to be low at baseline.[109–111]

Although the evidence for use of oral magnesium for asthma is mixed, overall it suggests a benefit, especially in those patients with low magnesium levels at baseline. Dosages in studies showing benefits have ranged from 200 to 300 mg per day in children and adolescents, and 340 to 450 mg per day in adults.

Pain

A systematic review and meta-analysis of 27 RCTs supports the use of IV magnesium sulphate as an adjunct to anaesthesia in reducing pain scores and analgesia use post-operatively.[112] Oral magnesium lozenges have also been shown to reduce post-operative sore throat.[113]

Two double-blind, placebo-controlled trials looked at the benefits of magnesium in neuropathic pain, one of which showed that IV magnesium, followed by oral magnesium, 500 mg per day, significantly reduced pain scores and increased motility in patients with chronic lower back pain.[114] However, another double-blind, placebo-controlled trial failed to show a significant benefit of magnesium, 330 mg as chloride per day, over placebo in neuropathic pain, although there was a significant improvement with regards to the frequency of pain paroxysms (attacks) and emotional impact in the magnesium group.[115] It is noteworthy that in the latter trial there were significant improvements in neuropathic pain in both the magnesium and the placebo groups.

A 2001 Cochrane review and meta-analysis based on three RCTs concluded that magnesium was more effective than placebo to provide pain relief in dysmenorrhoea.[116] A recent RCT in women with dysmenorrhoea also showed that IV magnesium alongside opium and buprenorphine reduced pain and improved quality of life.[117]

Magnesium levels tend to be lower in migraine sufferers, and there are a number of possible mechanisms by which magnesium may be involved in the pathogenesis of migraines.[118] A 2016 review and meta-analysis evaluated the use of magnesium in migraines, and found IV magnesium to be efficacious in acute attacks, and oral magnesium to reduce both frequency and intensity of migraines.[119] These findings have been confirmed by more recent clinical trials, one in adults, one in children, using 1000 mg per day (as oxide) and 75–375 mg per day depending on body weight (as oxide or glycinate), respectively.[120,121]

An interesting series of case studies also shows potential for high-dose oral magnesium to alleviate the pain caused by erythromelalgia,[122] a rare condition characterised by episodes of burning pain, usually in the extremities, and it is mentioned as a treatment option on the NHS website.[123]

Magnesium appears to be of benefit in a number of painful conditions, including neuropathic pain, dysmenorrhoea and migraines, with dosages used ranging from 500 to 1000 mg per day in adults, and 75 to 375 mg per day in children.

Fibromyalgia syndrome

Fibromyalgia syndrome is a complex pain syndrome that is also associated with insomnia, irritable bowel syndrome and other symptoms, and there is some overlap with CFS. There is limited evidence for the effectiveness of magnesium supplementation in FMS.

Two cross-sectional studies did not find a correlation between serum magnesium levels and FMS, but patients with FMS tend to have lower dietary magnesium intake.[124,125] An intervention study found women with FMS to have lower serum and erythrocyte magnesium levels, and compared the effectiveness of treatments with magnesium, 300 mg per day as citrate, amitriptyline, and magnesium plus amitriptyline. Whilst magnesium reduced some symptoms, amitriptyline on its own reduced almost all symptoms, with the combination being most effective.[126]

A double-blind, placebo-controlled trial of magnesium with malic acid showed no benefits during the 4-week blinded phase with a low dose of 150 mg magnesium and 600 mg malic acid, but showed significant benefits in the severity of pain and tenderness scores in an open-label extension of the study after 2 and 6 months, with a dose in excess of 400 mg magnesium and 1600 mg malic acid.[127]

Whilst the evidence is limited, magnesium at a dose of at least 300 mg per day could be trialled in patients with FMS.

Chronic fatigue syndrome

Mitochondrial dysfunction is thought to be an important factor in CFS, and magnesium is therefore commonly used in clinical practice in patients with CFS.

An early clinical trial found magnesium levels to be lower in people with CFS, and weekly magnesium sulphate injections to improve symptoms of pain, energy and emotional state.[128] However, no further research appears to have confirmed these promising results.[129]

Pre-eclampsia and pregnancy-induced hypertension (PIH)

Pre-eclampsia is a complication of pregnancy characterised by high BP, proteinuria and oedema. It can progress to eclampsia, which is a significant cause for perinatal and maternal morbidity and mortality. IV or intramuscular magnesium is recommended for women with pre-eclampsia by the World Health Organisation.[130]

Epidemiological studies suggest that women affected by pre-eclampsia or PIH have lower levels of magnesium.[131–134] However, a Cochrane review and meta-analysis in 2014 found no statistically significant reduction in pre-eclampsia with magnesium supplementation.[130] The authors pointed out that only two of the 10 studies reviewed were of high quality. A more recent RCT including 180 pregnant women showed that magnesium supplementation (200 mg per day) reduced the incidence of a number of pregnancy complications, including pre-eclampsia.[135]

The currently available evidence for benefits of magnesium to prevent pre-eclampsia is weak.

Depression

Two reviews and meta-analyses suggest an inverse relationship between magnesium levels or intake and the risk of depression.[136,137] This association has been confirmed in two more recent studies,[138,139] whilst in another study an association did not reach statistical significance.[140]

Whether oral magnesium supplementation is of benefit in patients with depression appears to depend on the dose and/or whether patients are magnesium-deficient: a 2018 double-blind, placebo-controlled trial showed no benefit of magnesium alongside fluoxetine.[141] Magnesium dosage was low (120 mg) compared with other clinical trials. A trial in post-partum depression did not find a benefit of magnesium at a dose of 64.5 mg (elemental, as sulphate).[142] On the other hand, 500 mg of magnesium (as oxide) was shown in a double-blind, placebo-controlled study to decrease depression scores in depressed patients with low magnesium levels.[143] Another RCT showed that 450 mg of magnesium (as chloride) was as effective as the tricyclic antidepressant imipramine in treating depression in elderly type 2 diabetics with hypomagnesaemia.

Although the evidence is mixed, at a dose of 450–500 mg per day, magnesium appears to be of benefit in patients with depression who have low magnesium levels.

Anxiety

The authors of a 2017 review on magnesium and anxiety concluded that magnesium may have a positive effect on mild to moderate anxiety, although they state that the current evidence base is poor. Only one of the eight trials reviewed in this article looked at magnesium on its own, the other studies included other botanicals or vitamin B6.[144]

Pre-menstrual syndrome (PMS)

The above review[144] also looked at the effects of magnesium on anxiety as a symptom of PMS, and found that four out of the seven relevant studies showed a positive effect of magnesium either on its own or in combination with vitamin B6, but also noted a number of methodological issues with the clinical trials reviewed.

A review and meta-analysis of observational studies looking at magnesium levels and PMS showed no significant association, although there was significant heterogeneity amongst the 13 studies reviewed; in particular, studies conducted outside of USA showed an inverse relationship between magnesium levels and PMS.[145]

A double-blind trial comparing magnesium, 250 mg per day (formulation not reported), magnesium plus vitamin B6, and placebo demonstrated that magnesium plus vitamin B6 was the most and placebo the least effective in relieving PMS symptoms.[146] The same research group also compared magnesium, 250 mg per day (formulation not reported), and vitamin B6 alone against placebo in subjects with PMS in another double-blind trial, and found a significant improvement in PMS scores in all three groups but more so in both the magnesium only and the vitamin B6 only groups than with placebo.[147] An open-label RCT also found significant benefits of magnesium, 250 mg per day as a modified-release formulation, in women with PMS but, due to lack of a placebo, results have to be interpreted with caution as there appears to be a significant placebo effect in PMS.[148]

Clinical research of magnesium for PMS is limited but promising, with a dose of 250 mg per day showing benefits.

Sleep

Lower intakes of magnesium are associated with shorter sleep time,[149] and magnesium appears to be involved in regulating circadian rhythms.[150] A small study in infants showed that serum magnesium levels were associated with sleep behaviour.[151]

However, evidence from clinical trials for the use of magnesium supplementation to improve sleep is limited. A double-blind, placebo-controlled study in elderly subjects with primary insomnia found that supplementing 500 mg magnesium (as oxide) improved both subjective and objective sleep parameters.[152] Baseline dietary magnesium intakes were low in this patient group. Another double-blind, placebo-controlled trial of magnesium, 225 mg per day (formulation not mentioned), in combination with melatonin and zinc also showed benefits in elderly subjects with insomnia.[153]

Although clinical research into magnesium and sleep is limited, a dose of 225–500 mg magnesium has been shown to improve sleep.

RLS/periodic limb movement in sleep (PLMS)

Low magnesium levels are associated with an increased incidence of PLMS,[154] and anecdotal evidence suggests magnesium supplementation to be of benefit.[155] However, there is only one open pilot trial published that reports benefits of oral magnesium, 301 mg per day (formulation not mentioned), for RLS and PLMS.[156] A double-blind, placebo-controlled trial of 28 patients, which formed the basis of a doctoral thesis, failed to show significant benefits of magnesium in RLS.[157]

At present there is insufficient evidence to show a benefit of magnesium for RLS.

Muscle cramps

Two reviews and meta-analyses found that magnesium did not help with leg cramps in the general population, but may have a small effect in pregnant women, although the evidence was considered weak.[158,159] A more recent trial on magnesium for nocturnal leg cramps in elderly subjects also found magnesium, 520 mg per day (as oxide), to have no benefits over placebo, although there was a strong placebo effect.[160]

The currently available evidence suggests that magnesium has no benefit for leg cramps.

Constipation

Magnesium salts act as osmotic laxatives,[161] and are used for both bowel clearance in preparation for procedures such as colonoscopies and in the management of chronic constipation. Low intake of magnesium has been shown to be associated with an increased risk of constipation independent of fibre intake.[162]

Magnesium and sulphate-rich mineral water has been shown in a number of double-blind, placebo-controlled clinical trials to be beneficial in chronic/functional constipation.[163–166] A recent double-blind, placebo-controlled trial also reports good results with supplementation of magnesium oxide (1.5 g per day, equivalent to 915 mg elemental magnesium) in patients with functional constipation.[167] Another trial in elderly patients with constipation showed benefits of supplementation with magnesium hydroxide.[168]

Magnesium salts have also been shown to help with constipation in children and infants in a number of clinical trials, both on their own and in combination with other compounds.[169–172]

Prolonged use of high doses of magnesium, as commonly used in constipation, can lead to hypermagnesaemia, especially in those with kidney disorders, and monitoring of serum magnesium levels is advised.[173,174]

Whilst there is good evidence for the use of magnesium in constipation, the dosages needed are high and could cause harm with prolonged use.

Dyspepsia

Magnesium salts, in particular magnesium hydroxide, carbonate and trisilicate, are commonly used in antacids, either on their own or in combination with aluminium salts and/or alginates (which coats the surface of the stomach). The magnesium salts can help relieve symptoms of indigestion, gastro-oesophageal reflux, gastritis and gastric ulcers. They tend to work quickly, but are not recommended for long-term use as they do not deal with the underlying cause, and can have side-effects and drug interactions.[175–177]

Dose Recommendations

The mineral content of fruit and vegetables has declined significantly over past decades,[178,179] and processing of foods further reduces their magnesium content. Surveys show that significant proportions of the population are not getting adequate levels of magnesium through their diet (see above). Supplementing magnesium on a daily basis to reduce the risk of developing chronic disease appears to be prudent. The Linus Pauling Institute, Oregon State University, USA, recommends a supplemental dose of 100 mg per day, alongside a magnesium-rich diet.[180] In view of the likely shortfall, this seems to be a reasonable dose for preventive purposes.

Clinical studies that looked at therapeutic use of magnesium in various conditions have used a range of dosages, but the most commonly used doses were between 300 and 400 mg per day.

Safety

The most common side-effects of excessive magnesium intake are gastrointestinal disturbances, in particular diarrhoea. Hypermagnesaemia, defined as a serum magnesium level above 2.6 mg/dl, is rare and is most commonly seen in patients with kidney disease. Caution is therefore advised for the use of magnesium supplements in

patients with kidney disease. Excessive use of magnesium, usually as a laxative or antacid, can also cause hypermagnesaemia at intakes over 2500 mg magnesium (elemental). Symptoms include weakness, hypotension, respiratory depression, and can lead to cardiac arrest.[181–183]

Magnesium from food does not induce diarrhoea or other side-effects. The upper tolerable limit (UTL) of magnesium from supplements is based on the amount that does not induce diarrhoea, and is in addition to intakes from food.

- The European Food Safety Agency (EFSA) set a UTL for magnesium of 250 mg for adults, including pregnant and lactating women, and children from 4 years.[183]
- The US Food and Nutrition Board, Institute for Medicine, set a UTL for magnesium of 350 mg for adults, including pregnant and lactating women, and children from 9 years, 110 mg for children aged 4–8 years, and 65 mg for children aged 1–3 years.[21]

Magnesium supplements can interact with a number of medications:[21]

Bisphosphonates (drugs to treat osteoporosis): magnesium can decrease absorption. Magnesium should be administered at least 2 hours apart.

Tetracycline and quinolone antibiotics: these can form complexes with magnesium, and should therefore be administered at least 2 hours before or 4–6 hours after the magnesium supplement.

Diuretics: loop and thiazide diuretics, including furosemide and bumetanide, hydrochlorothiazide and ethacrynic acid, can deplete magnesium and lead to hypomagnesaemia. Potassium-sparing diuretics, such as amiloride and spironolactone, on the other hand, also have a magnesium-sparing effect and can therefore raise magnesium levels.

PPIs: long-term use of PPIs can lead to hypomagnesaemia, and magnesium levels should be monitored in such patients.

Levodopa/carbidopa: a recent study showed that magnesium oxide may significantly reduce absorption of levodopa/carbidopa.[184]

Digoxin: magnesium-based antacids interfere with the absorption of digoxin.[185]

Sulphonylureas (type of anti-diabetic drug): magnesium-based antacids alter intestinal pH, and can therefore lead to an increased absorption of sulphonylurea drugs, potentially leading to hypoglycaemia.[186,187]

Conclusion

Magnesium has been shown to be of benefit in a range of conditions, including diabetes, hypertension, metabolic syndrome, pain and for bone health. The most commonly used dosages in clinical trials have been in the range of 300-400 mg per day, which is generally considered safe. The most common side effect with an excessive dose is diarrhoea. Caution should be exercised in patients with kidney disease and magnesium can interact with a number of medications.

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Coenzyme Q10: A Review of Clinical Use and Efficacy

Karin Elgar

Abstract

Coenzyme Q10 (CoQ10) plays an essential role in energy production as part of the mitochondrial electron transfer chain. It also has antioxidant functions and is important for gene regulation, especially of genes involved in cell signalling, metabolism, inflammation, transport and transcription control. Whilst we can obtain small amounts from our diet, most CoQ10 is synthesised in our bodies, which is why it is not considered to be a vitamin. Production declines with age and may also be impaired through illness and/or certain medications, making supplementation an interesting intervention. Although clinical research has been mixed in some indications, CoQ10 supplementation has been found to be a safe and effective intervention in a variety of conditions, including cardiometabolic disorders, fibromyalgia syndrome, migraine and male infertility.

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Introduction

Coenzyme Q10 (CoQ10), also called ubiquinone, is a fat-soluble, vitamin-like substance which, as the name suggests, is ubiquitous to all cellular membranes in our bodies. It plays an essential role in mitochondrial function as part of the electron transfer chain, which produces adenosine triphosphate (ATP), the energy currency of our cells. CoQ10 also has important antioxidant functions, preventing oxidation of lipids, proteins and DNA by recycling other antioxidants, including vitamins C and E, increasing production of antioxidant enzymes, such as superoxide dismutase, and preserving nitric oxide (NO).[1] CoQ10 also plays a role in regulating gene expression, in particular of genes involved in cell signalling, metabolism, inflammation, transport and transcription control.[2]

We can obtain CoQ10, although generally in small amounts only, through our diet, in particular from organ meats like heart and liver, which contain in the range of 22–282 mg/kg.[3] CoQ10 is also synthesised in our bodies via the mevalonate pathway, which is also involved in the synthesis of cholesterol,[1] and is therefore not considered to be a vitamin. Dietary supplements provide CoQ10 in either the oxidised form (ubiquinone) or the reduced form (ubiquinol); where publications have specified which form was used, this is mentioned in the section: **'Clinical uses'**. As CoQ10 switches rapidly between these two forms, the choice of supplement appears to be less important than the lipid carrier or other excipients that affect absorption and/or bioavailability.[4] There also appears to be significant variation in terms of absorption and bioavailability between individuals.[4] Being fat-soluble, CoQ10 is best taken with a meal, which increases absorption threefold.[2]

Endogenous CoQ10 levels depend on rates of both production and consumption. Levels of CoQ10 decline as we age, but can also decrease through illness or use of certain medications, for example, statins. Severe deficiency can be due to genetic defects as, for example, seen in cerebellar ataxia, Leigh syndrome and infantile encephalopathy.[2]

CoQ10 can be measured in serum and plasma, although it is unclear how well this correlates with tissue concentrations.[5] Establishing CoQ10 levels may help identify those who would benefit most from supplementation, and regular testing may also be useful to monitor the efficacy of supplementation in view of both inter-individual variability of absorption and variable bioavailability of different formulations.[5]

In view of its important role in energy production, gene regulation and as an antioxidant, CoQ10 supplements have become popular for a large range of clinical uses. The aim of this paper is to review the evidence from human clinical trials.

Clinical Uses

Athletic performance

Due to its important role in energy metabolism and as an antioxidant, CoQ10 has received much attention in sports nutrition, both in untrained and trained individuals, to boost performance and reduce oxidative stress and muscle damage.

In 2003, a review of 11 clinical trials investigating CoQ10 for athletic performance found mixed results, with six studies showing benefits and five showing no benefits.[6] The authors noted that those articles reporting nil effects were more likely to be published in peer-reviewed journals than those reporting positive results, more of which were published as conference proceedings only. The authors of the review also pointed out that all studies only included small numbers of participants (maximum 28) and were of different designs, making conclusions difficult. Since then, more randomised-controlled trials (RCTs) have been published but, again, most of them were small in size.

In elite athletes, the results from mostly small double-blind, placebo-controlled trials are

largely positive, with CoQ10 supplementation having positive effects on oxidative stress, inflammatory markers and performance.[7,8,9,10] In relation to muscle damage, two studies showed inconsistent results – with one showing benefits[11] and one not.[12] Most studies used 300 mg per day for 2–4 weeks.

In non-elite, trained and untrained people, the evidence is mixed, with some studies reporting benefits in terms of inflammation,[13] bone formation,[14] oxidative stress/antioxidant status,[15,16,17,18] performance[19,20] and muscle damage,[21] whilst others found no benefit for performance,[15,22,23,24,25,26] muscle damage[15,22,27,28] and oxidative stress.[22,23,24,27,28] One small study even found increased muscle damage and poorer performance with CoQ10 supplementation.[29,30] Dosages used ranged from 90 to 300 mg per day, and duration of supplementation ranged from 8 days to 12 weeks. Nil results have been observed with low as well as with higher dosages.

It should be noted that most of the trials were small and results may therefore have failed to reach statistical significance. Specific outcomes studied in the trials varied widely, as did study designs, making it difficult to compare trials and explain the contradictory findings. Both ubiquinone and ubiquinol have been used in these trials, and results were inconsistent for both compounds.

Based on the above studies, a dosage recommendation would be 300 mg per day for at least 4 weeks.

Bipolar disorder

Bipolar disorder (BPD) is a chronic and recurrent mental health disorder characterised by extreme changes in mood with episodes of mania and major depression.[31] Mitochondrial dysfunction, oxidative stress and inflammation are thought to play important roles in the development of the condition.[32] As CoQ10 can affect all three, a couple of RCTs have investigated its potential benefits alongside usual treatment regimes.

One open-label study in 32 older patients with BPD used 400 mg per day for 2 weeks, and then the dose was titrated up to 800 mg per day for another 2 weeks. Significant improvements were seen within 2 weeks. After 4 weeks, the MADRS score (Montgomery Asberg Depression Rating Scale, a scale of 0–60) had improved by 8 points.[33] A similar size effect on MADRS score was seen in a double-blind, placebo-controlled trial of 69 patients, using 200 mg CoQ10 per day for 8 weeks, with a gradual improvement.[32] The latter study also observed a decrease in oxidative stress and inflammatory markers, suggesting that the antioxidant and anti-inflammatory properties of CoQ10 may explain the mechanism of its benefits in BPD.[34]

Although evidence is limited, it appears that CoQ10 is of benefit alongside the usual treatment in BPD, and a dose of 200 mg per day for 8 weeks has been used successfully in clinical trials.

Cardiovascular disease and risk factors

Cardiovascular disease (CVD) is a general term for diseases that affect the heart and blood vessels, and is collectively one of the main causes of death in Western countries. CVD usually develops over many years, and risk factors include hypertension (high blood pressure), abnormal blood lipids, smoking and poor diet.

Few clinical trials on dietary supplements, like CoQ10, run for long enough to ascertain their potential benefits in reducing mortality and morbidity from CVD. Most studies therefore investigate risk factors as an outcome, and the ones relevant to CoQ10 are discussed below.

Two longer-term, double-blind clinical trials that reported on cardiac deaths and cardiovascular events have shown significant benefits of CoQ10, the largest and longest one being the Q-SYMBIO trial. Both are discussed below.[35,36]

Because CoQ10 has also been shown to improve a range of risk factors (even in the face of some mixed/contradictory evidence, see below), supplementation of 120–300 mg for at least a year could be beneficial for people with or at elevated risk of CVD.

Dyslipidaemia

Dyslipidaemia, abnormal levels of blood lipids including triglycerides and total, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, is considered to be an important risk factor for CVD.

A meta-analysis of 21 RCTs, involving 1039 participants with metabolic disorders, found that CoQ10 supplementation led to a significant decrease in triglycerides, but did not affect total, LDL or HDL cholesterol levels, with higher dosages (200 mg) appearing to be more beneficial than lower dosages.[37] Another meta-analysis,[38] including eight RCTs with a total of 526 patients with coronary artery disease (CAD), found that in this patient population, CoQ10 significantly lowered total cholesterol and increased HDL cholesterol but had no effect on triglycerides, whilst improvements in LDL cholesterol and lipoprotein(a) failed to reach statistical significance. Dosages in the trials included in the meta-analyses ranged from 100 to 300 mg per day for 4–12 weeks in most studies, with two studies lasting 24 and 48 weeks, respectively.

Only one of the studies in the above meta-analyses had more than 65 study subjects: a double-blind study comparing CoQ10, 120 mg per day, versus B vitamins for 48 weeks in 144 patients after myocardial infarction.[35] This study showed that CoQ10 increased HDL cholesterol, and total to HDL cholesterol ratio decreased more than the control (B vitamins). Patients in the CoQ10 group also had significantly less cardiac events and cardiac deaths than the control group. A more recent double-blind, placebo-controlled study of 101 patients with dyslipidaemia showed that CoQ10, 120 mg per day for 24 weeks, significantly reduced triglycerides and LDL cholesterol.[39]

Whilst results are contradictory, the overall evidence suggests that CoQ10 may be beneficial in terms of improving blood lipids.

The two biggest RCTs saw beneficial effects at a dosage of 120 mg per day for 24–48 weeks, suggesting that (to see significant benefits) supplementation should last at least 6 months.

Possible mechanisms include the beneficial effect of CoQ10 on glucose/insulin metabolism (see below), and its ability to reduce oxidative stress and regulate expression of genes involved in lipid metabolism.[37,38]

Endothelial dysfunction

The endothelium is the inner layer of blood vessels, and it controls vascular relaxation and contraction. In endothelial dysfunction there is an imbalance between vasodilating substances (which widen the blood vessels) and vasoconstricting substances (which narrow the blood vessels). NO plays an important role in mediating this vasodilation and constriction. Endothelial dysfunction is involved in the development of atherosclerosis and, as such, is a risk factor for CVD. High blood pressure, smoking and diabetes are thought to contribute to endothelial dysfunction.[40]

A 2012 meta-analysis of five studies, totalling 194 participants with endothelial dysfunction, found that CoQ10 was significantly better than placebo in improving endothelial function, determined as flow-mediated dilation.[41] Dosages used in the trials ranged from 150 to 300 mg per day, and study durations from 4 to 12 weeks. Since then, four double-blind, placebo-controlled trials have confirmed the benefits of CoQ10 in endothelial dysfunction,[42,43,44,45] of which three reported to have used ubiquinol.[42,44,45]

Dosages between 150 mg and 400 mg for at least 4 weeks have shown benefits, although longer duration has led to greater improvements.

The mechanisms involved are thought to be increased NO bioavailability, anti-inflammatory activity and enhanced LDL antioxidant protection.[41,42]

Heart failure

Heart failure, also called congestive heart failure, occurs when the heart muscle does not pump blood as efficiently as it should because it is too weak or stiff, resulting in symptoms such as shortness of breath, fatigue, and swollen ankles and legs. Common causes include high blood pressure and narrowed arteries supplying the heart muscle itself (CAD).

Heart failure can be divided into heart failure with reduced (less than 40%) ejection fraction (the percentage of the blood in the left ventricle that is pumped out with each heartbeat) and with preserved ejection fraction, where ejection fraction is normal or at least above 40%, and it is the relaxation, rather than the contraction, of the left ventricle that is affected.[46]

A 2017 meta-analysis of 14 RCTs with 2149 patients found that CoQ10 significantly reduced mortality and increased exercise capacity compared with placebo, whilst improvements in left heart ejection fraction and New York Heart Association (NYHA) cardiac function classification failed to reach statistical significance.[47] A number of reviews on the topic have also come to the conclusion that CoQ10 is effective in reducing mortality and morbidity in patients with heart failure.[48,49,50,51]

By far the largest double-blind, placebo-controlled trial of CoQ10 in heart failure is the Q-SYMBIO trial,[36] where 420 patients with moderate to severe heart failure received either CoQ10, 100 mg three times per day, or placebo for 2 years. Whilst there were no significant differences in short-term outcomes, only 15% of patients on CoQ10 had major cardiovascular events (the primary end-point of the study) compared with 26% of patients who received placebo. Both cardiac and all-cause mortality were significantly lower in the CoQ10 group, who also experienced a significant improvement of NYHA class compared with placebo. In this trial, the placebo group had more adverse events than the CoQ10 group.

CoQ10 has also shown benefits in children with dilated cardiomyopathy.[52,53,54] Dosages ranged from 3 to 10 mg per kg of body weight (mg/kg) per day, and duration of supplementation ranged from 24 weeks to 9 months. One of the studies reported the use of ubiquinol (10 mg/kg for 24 weeks).[53]

Overall, it appears that higher dosages, for example, 300 mg per day, and longer duration of supplementation may be needed to get the full benefits in terms of heart function.

The mechanisms by which CoQ10 exerts its benefits in heart failure are probably multiple, including an increased energy production in the failing heart, reduced oxidative stress (which tends to be high in these patients) and improved endothelial function (see also above).[36]

Hypertension

Hypertension is the largest known risk factor for heart disease and, globally, hypertension is the second biggest risk factor for overall mortality and morbidity, after poor diet.[55] In 2015, one in four men and one in five women worldwide had high blood pressure.[56]

A couple of early open-label studies showed significant blood-pressure-lowering effects of CoQ10 in patients with essential hypertension: one showed a reduction from 164.5 to 146.7 mmHg for systolic and from 98.1 to 86.1 mmHg for diastolic blood pressure;[57] whilst in the other, more than half of patients receiving CoQ10 were able to stop their anti-hypertensive drugs, whilst only 3% had to add another drug after 1–6 months of supplementation.[58]

A Cochrane review of three double-blind, placebo-controlled trials in 2016 concluded that the evidence suggests that CoQ10 does not lower blood pressure; however, the meta-analysis only included two of these studies with a total of 50 participants, the third study was excluded due to high risk of bias.[59] Both studies used 100 mg per day for 10 or 12 weeks.

In 2018, a review and meta-analysis of 17 RCTs, totalling 684 patients with hypertension and metabolic disease, found that overall there was a statistically significant reduction in systolic blood pressure, whilst reduction in diastolic blood pressure did not reach statistical significance.[60] Whilst seven of the individual trials found benefits of CoQ10 on blood pressure, the other 10 did not find any effect. Studies using dosages between 100 and 150 mg per day found better results than those using more than 150 mg per day. One study using 900 mg per day found no effect, although this was of shorter duration (4 weeks) than most other studies (8–24 weeks). The authors do not discuss a possible explanation for this finding, other than that a limitation of many studies is that dietary intakes and/or baseline CoQ10 levels are not always established.[60]

Since then, another double-blind, placebo-controlled trial with 101 dylipidaemic patients not taking any hypoglycaemic or hypolipidaemic drugs found that CoQ10, 120 mg per day for 24 weeks, reduced systolic and diastolic blood pressure from 134 mmHg to 125 mmHg, and from 85 mmHg to 78 mmHg, respectively, compared with a reduction from 129 mmHg to 127 mmHg and from 82 mmHg to 80 mmHg, respectively, with placebo. Beneficial effects were seen at 12 weeks.[39]

CoQ10 has also been studied alongside and/or against omega-3 fatty acids with conflicting results. Two studies showed that CoQ10 (150 mg or 200 mg per day) significantly reduced blood pressure alongside either omega-3 fatty acids and/or hypolipidaemic drugs in patients with hypertriglyceridaemia,[61,62] whilst another study found no effects of CoQ10 either alone or with omega-3 fatty acids on blood pressure in patients with chronic kidney disease.[63] Dosages of polyunsaturated fatty acids (PUFAs) were 3000 mg PUFAs (not further described),[61] 2520 mg omega-3 PUFAs [dose of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) not reported],[62] and 1840 mg EPA and 1520 mg DHA per day,[63] respectively.

The reasons for the contradictory results are unclear. Overall, there appears to be a beneficial effect of CoQ10 in hypertension, with dosages of 100–150 mg being effective.

Some authors have hypothesised that the benefits may be due to improvements in myocardial bioenergetics through CoQ10, which would suggest that longer periods (more than 1 month) of supplementation may be required to see effects.[58] Other authors suggest that the benefits are mediated by the antioxidant effects of CoQ10, which may improve endothelial function via the NO cycle.[60]

Diabetes and dysglycaemia

People with type 2 diabetes mellitus (T2DM) have lower CoQ10 levels than healthy people, and supplementation has been shown to increase levels.[64]

Three meta-analyses evaluated the potential of CoQ10 on glycaemic control, and found significant benefits in patients with diabetes,[65,66] and patients with diabetes and/or other cardiometabolic conditions.[67] CoQ10 has also been shown to improve other risk factors in people with T2DM, such as biomarkers for endothelial function, inflammation, antioxidant status and lipid profiles, although not all studies found improvements in all markers.[39,45,68,69,70] Both the ubiquinone[70] and the ubiquinol[45,68] forms have shown benefits.

Dosages used were generally in the range of 100–300 mg per day, and studies lasted for 4–24 weeks.

The mechanism involved is thought to be reductions in oxidative stress, leading to better mitochondrial function, which may in turn improve glycaemic control in patients with T2DM.[65]

Fatigue

Due to its importance in energy production as part of the mitochondrial electron transfer chain, it is intuitive to consider CoQ10 to alleviate fatigue or enhance energy in both healthy people and those with conditions associated with fatigue. However, the benefit of CoQ10 for fatigue appears to differ across patient populations, and thus its use may benefit from personalisation.

Fatigue in healthy adults

Two studies looked at the effect of CoQ10 on fatigue in response to cognitive or physical tasks in healthy volunteers with or without mild fatigue, and found significant reductions in fatigue.[20,71] Smaller effects were seen with 100 mg per day, and larger effects with 150 mg or 300 mg per day, suggesting that higher dosages are more effective. Improvements with 300 mg were seen after only 8 days of supplementation, whilst the other study used 100 mg versus 150 mg for 12 weeks. Improvements were mirrored by increases in serum CoQ10 levels.

A study using 200 mg CoQ10 for 12 weeks in healthy but obese adults found an improvement in fatigue, although this failed to reach statistical significance when compared with placebo.[72]

Two more studies that looked at the effect of CoQ10 on exercise performance found benefits in terms of exercise performance but not fatigue.[10,19] Dosages used were 300 mg for 1 month and 100 mg for 8 weeks, respectively.

Only two articles specified whether the reduced or oxidised form of CoQ10 was used: one study using ubiquinol, 100 mg or 150 mg per day, found significant improvements;[71] whilst in one study using ubiquinone, 200 mg per day, improvements were not statistically significant.[72]

Overall, the evidence for the use of CoQ10 to reduce fatigue in generally healthy people is contradictory. Dosages of 150–300 mg per day may be needed to see an effect. Although benefits of 300 mg per day for 8 days have been seen, a longer duration may be necessary to obtain significant results.

Chronic fatigue syndrome

Chronic fatigue syndrome (CFS) is a complex, poorly understood disorder, with extreme fatigue being the most common symptom. Mitochondrial dysfunction is thought to play an important role in CFS, and CoQ10 is therefore a likely candidate for supplemental support.

However, only two clinical trials have assessed the effectiveness of CoQ10 on its own in CFS. One open-label study found no benefits in terms of clinical outcomes (including fatigue) or oxidative stress with CoQ10 (as ubiquinol), 150 mg per day for 8 weeks.[73] A double-blind, placebo-controlled trial by the same investigators, using the same dosing regimen but for 12 weeks, found small but statistically significant improvements in arithmetic tasks, awakening at night and autonomic nervous function, but not fatigue or depression.[73] In both studies, patients had low plasma levels of CoQ10 before the start of supplementation, and CoQ10 supplementation increased blood levels.

Two further studies looked at CoQ10 alongside nicotinamide adenine dinucleotide (NADH, another important nutrient for cellular energy production). One study, using 50 mg CoQ10 and 5 mg NADH per day for 8 weeks, found no significant improvements in terms of fatigue,[74] whilst the other, using 200 mg CoQ10 and 20 mg NADH per day for 8 weeks, found significant improvements in both fatigue and biochemical markers.[75]

The dosages used in all these trials are low compared with those used in other studies, for example, for fibromyalgia syndrome (FMS; see below), which may be the reason for the lack of efficacy in some of these trials. It is also important to bear in mind that, being a complex disorder, it would be unlikely for one nutrient alone to lead to significant improvements in CFS. The fact that a combination of CoQ10 and NADH, with CoQ10 at 200 mg per day, offered some benefit despite the fairly low dose is encouraging.

A dose of at least 200 mg CoQ10 for at least 8 weeks and ideally in combination with other relevant nutrients to support mitochondrial function could be suggested in CFS.

Fibromyalgia syndrome

FMS has a lot of overlap with CFS, with fatigue being a prominent symptom alongside widespread pain. As for CFS, the exact causes are unknown, but mitochondrial dysfunction and oxidative stress are thought to play important roles.[76]

A number of clinical trials have shown evidence for a significant benefit of CoQ10 (as ubiquinone) in this patient population. The earliest evidence comes from an open-label study of CoQ10, 200 mg per day, alongside Ginkgo biloba, which showed a significant gradual improvement in quality of life over the 12-week study period.[77]

Following a case series where impressive results with CoQ10 supplementation in four patients with FMS were found,[78] Cordero *et al*. in Spain conducted a number of controlled studies that showed a significant benefit of CoQ10, 100 mg three times per day, in patients with FMS, with a halving of pain scores and significant reductions in depression, headaches, tender points and fatigue.[79,80] A small double-blind, placebo-controlled trial by these investigators evaluated a host of biochemical and other disease markers to elucidate possible mechanisms. They found that, compared with healthy controls, FMS sufferers had lower levels of CoQ10 and ATP, increased oxidative stress, inflammation and mitochondrial dysfunction, which were to some extent explained by changes in gene expression.[81,82,83] In these studies, supplementation with CoQ10, 100 mg three times per day, improved inflammation, oxidative stress and mitochondrial function, leading to improvements in fatigue by 50%. Serotonin levels were also increased, with a reduction in depression.[83]

A more recent double-blind, placebo-controlled study also found beneficial effects of CoQ10, 300 mg per day for 40 days, alongside pregabalin (an anti-convulsant and anti-anxiolytic drug that is also used for neuropathic pain, FMS and other indications) in patients with FMS, with greater reductions in pain, anxiety and brain activity, mitochondrial oxidative stress and inflammation than pregabalin alone.[84]

A Japanese study in children aged 8–18 years with juvenile FMS found that patients had significantly lower plasma levels of ubiquinol-10, and an increased ratio of ubiquinone-10 to total CoQ10 (%CoQ10), compared with healthy controls, suggesting that FMS is associated with CoQ10 deficiency and increased oxidative stress.[85] Supplementation with CoQ10 (as ubiquinol), 100 mg per day, led to significant improvements in biochemical markers as well as fatigue, but not pain or quality of life. Beneficial effects were seen as early as within 2 weeks. The authors suggested that higher dosages might give better benefits in this paediatric patient population.

Overall, the evidence for the use of CoQ10 in FMS is good, with a dose of 300 mg per day for at least 3 months suggested. Based on the evidence above, as with CFS, combining CoQ10 with other nutrients or botanicals may give even better results, although relevant studies are lacking.

There appear to be a number of mechanisms involved in the beneficial effects of CoQ10, including improved mitochondrial function, reduced inflammation and oxidative stress, and increased serotonin levels, which may be due, at least in part, to modulation of gene expression.[81,82,83]

Fertility and pregnancy

Male subfertility

Sperm cells, in particular their membranes, are susceptible to oxidative damage, and such damage is thought to be responsible for 30–80% of cases of male subfertility.[86] The antioxidant properties of CoQ10 could therefore be expected to be beneficial to sperm health, and therefore male fertility.

A 2020 meta-analysis of three double-blind, placebo-controlled trials, totalling 296 patients with reduced sperm motility only or reduced sperm motility and count, found that CoQ10, at dosages of 200–300 mg per day for 12–26 weeks, significantly increased sperm counts, motility and forward motility.[87] Only one of

the trials reported pregnancy rates, which was 6/28 in the CoQ10 group and 3/27 in the placebo group.[88]

Several studies, RCTs and uncontrolled studies not included in the above meta-analysis have also consistently shown improvements in sperm counts and motility, and some, but not all, have found improvements in sperm morphology where it had also been abnormal.[89,90,91,92,93,94,95] Only one of these trials, an open-label, prospective study, reported pregnancy as an outcome and found a 34.1% pregnancy rate within a mean of 8.4 months.[96]

The evidence is overwhelmingly in favour of CoQ10 in male subfertility and the most commonly used dose was 200 mg per day, although one study compared a daily dose of 200 mg with 400 mg and found better results with the higher dose.[91] As it takes 3 months for sperm cells to mature, duration of supplementation should be a minimum of 3 months. Study durations ranged from 3 to 12 months, with benefits seen after 3 months. All studies that specified the form of CoQ10 had used the ubiquinol form.[89,91,92,93,95]

The mechanism of action is thought to be the ability of CoQ10 to increase antioxidant capacity, which has indeed been observed in some of the above studies.[89,90,91,94]

Female subfertility

A number of studies have also investigated female subfertility, most of them focussing on CoQ10 supplementation prior to assisted fertilisation, with promising results in terms of fertilisation rates, retrieved egg cells and reduction in number of abnormal chromosome counts, although improved pregnancy rates on the whole failed to reach statistical significance.[97,98,99] Dosages in these studies were 600 mg per day for at least 1 month.

The use of CoQ10 for women whose subfertility is due to polycystic ovarian syndrome (PCOS) is discussed below.

Pre-eclampsia

Pre-eclampsia is a pregnancy-related condition, characterised by hypertension, proteinuria (protein in urine) and oedema, which is potentially life-threatening to both mother and baby. Mitochondrial dysfunction, leading to lack of cellular energy and increased free radicals/oxidative stress, has been considered to be an underlying mechanism, and abnormal CoQ10 levels have been observed in pre-eclampsia, suggesting CoQ10 supplementation may be beneficial for prevention.[100]

Only one double-blind, placebo-controlled trial has investigated supplementation with CoQ10, 200 mg per day from week 20 of pregnancy until delivery, in 197 women at increased risk of pre-eclampsia:[101] 25.6% of women in the placebo group and 14.4% of women in the CoQ10 group developed pre-eclampsia, a statistically significant result.

Migraine

Whilst the causes of migraines are not completely understood, vascular and neuronal dysfunction are thought to play important roles, and may be due to impaired oxygen metabolism, oxidative stress and inflammation.[102] Being able to positively affect all three, CoQ10 has been considered as a prime candidate for prevention of migraines. Positive influences of CoQ10 on inflammatory markers in patients with migraines have been observed in parallel with symptomatic improvements.[103]

Two double-blind, placebo-controlled and three open-label studies have evaluated the efficacy of CoQ10 in the prevention of migraines in adults, and all found significant benefits in terms of reducing the number of attacks per month.[103,104,105,106,107] The severity and duration of attacks also significantly decreased, although this did not reach statistical significance in all studies. Up to 80% of study participants had improvements of more than 50% in frequency or days with migraines.

Improvements have been seen at dosages as low as 100 mg per day,[105] although dosages of up to 600 mg per day have been used, and benefits have been seen within 4 weeks with further improvements over the following 2–3 months of supplementation.

CoQ10 has also been studied in combination with other nutrients, namely curcumin,[108] L-carnitine,[109] feverfew and magnesium,[110] and beneficial effects of these combinations were reported.

Two clinical trials evaluated the benefits of CoQ10 in children and adolescents with migraines. In a double-blind, placebo-controlled crossover study, participants in both the active CoQ10 (100 mg per day) as well as the placebo group experienced very significant improvements in frequency, duration and severity of migraines. Within the first 4 weeks, frequency of migraines reduced from 19 to 11 in the CoQ10 group, and from 21 to 14.5 in the placebo group. Further improvements were seen over the following 3 months, but differences between groups were only statistically significant for frequency at 4 weeks.[111]

An open-label study assessed 1556 consecutive 3–22 year olds with migraines for their serum CoQ10 level, and found that almost a third were below the reference range. Two-hundred and fifty-two patients with low CoQ10 levels started to supplement at a dose of 1–3 mg/kg per day. After an average follow-up of just over 3 months, CoQ10 levels had significantly increased in these patients, migraine frequency reduced from 19.2 to 12.5, and 46.3% of patients reported a reduction in migraines of more than 50%.[112] Due to lack of blinding and placebo control, it is difficult to conclude whether these improvements were due to supplementation or not, as a very significant placebo effect has been demonstrated in this population.[111]

The evidence supports the use of CoQ10 for migraines in adults, with dosages of at least 100 mg per day for at least 4 weeks. For children and adolescents, it is unclear whether benefits observed are due to a placebo effect or the active compound.

Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is caused by a build-up of fat within liver cells, and risk factors include obesity/overweight, metabolic syndrome and T2DM.[113]

Two double-blind, placebo-controlled trials investigated the use of CoQ10, 100 mg per day, in patients with NAFLD. One trial, which lasted 12 weeks, found improvements in liver aminotransferases (a marker of liver function), inflammatory markers and NAFLD grade.[114] The other trial also found improvements in one aminotransferase and a marker for oxidative stress, but other biochemical markers failed to reach statistical significance, possibly due to the short, 4-week duration of the trial.[115]

Although evidence is limited, CoQ10, at a dose of at least 100 mg per day for at least 12 weeks, appears to be a valuable option for people with NAFLD, especially due to the fact that these patients also commonly have other co-morbidities and biochemical abnormalities for which CoQ10 has also been shown to be beneficial.

The mechanisms for the benefit of CoQ10 in NAFLD are most likely its anti-inflammatory and antioxidant effects.[114]

Neurodegenerative diseases

Alzheimer's disease

Oxidative stress and mitochondrial dysfunction are thought to play a role in the development of Alzheimer's disease, and preclinical studies have shown CoQ10 to have neuroprotective effects.[2] However, there is only one small double-blind, placebo-controlled trial in humans that looked at the effects of CoQ10, 400 mg three times per day for 16 weeks, on biomarkers in the cerebrospinal fluid, which found CoQ10 to be of no benefit with regards to biomarkers or cognitive function.[116]

Multiple sclerosis

Multiple sclerosis (MS) is a chronic inflammatory condition of the central nervous system, and oxidative stress is thought to play an important role in the development of MS lesions, making CoQ10 a likely candidate for intervention.

One double-blind, placebo-controlled trial of 45 patients with relapsing–remitting MS found significant improvements in fatigue and depression with 500 mg CoQ10 per day for 12 weeks.[117] This study also found a significant decrease in oxidative stress, an increase in antioxidant capacity and a reduction in inflammatory, but no change in anti-inflammatory, markers.[118,119]

An open-label study using CoQ10, 200 mg per day for 12 weeks, found similar results, reduced oxidative damage and a shift towards a more anti-inflammatory milieu in the peripheral blood, and small but significant clinical improvements in depression, pain, disability score and fatigue.[120]

These are promising results, although unfortunately no data on longer-term supplementation are available. A dose of 200–500 mg CoQ10 per day for at least 3 months could be suggested.

Parkinson's disease

Mitochondrial dysfunction and oxidative stress are thought to play a role in the development of Parkinson's disease (PD).[121] Patients with PD have been shown to have higher rates of CoQ10 deficiency in peripheral blood mononuclear cells (a marker of general CoQ10 deficiency)[122] and, more specifically, in cells of the cortex region of the brain.[123] It therefore seems logical that improving CoQ10 status through supplementation may be of benefit in patients with PD.

Indeed, a number of RCTs have been conducted into the potential use of CoQ10 in PD. In 2011, a Cochrane review and meta-analysis[124] found some benefits of high-dose CoQ10 in patients with PD; however, this review was later withdrawn due to a number of methodological shortcomings.[125]

Since then, two more meta-analyses have not found any benefit of CoQ10 on motor function or progression of disease.[121,126] A small double-blind, placebo-controlled pilot study found some benefit of CoQ10 (as ubiquinol) in patients experiencing 'wearing off' (where levodopa treatment stops controlling symptoms satisfactorily), but not in early PD patients not yet treated with levodopa.[127]

An RCT combining CoQ10 (300 mg per day, as ubiquinone) and carnitine (10 g per day) found the combination to significantly slow cognitive decline but not any other PD symptoms over placebo.[128]

Overall, to date, the evidence to support the use of CoQ10 to improve PD symptoms or progression is weak.

Periodontal disease

Periodontal, or gum, disease is thought to be caused by bacterial pathogens causing an inflammatory response with increased production of reactive oxygen species, aggressive molecules that cause tissue damage, leading to inflammation, receding gums and potentially tooth loss. Antioxidants like CoQ10 are thought to reduce this damage.[2] Decreased levels of CoQ10 have been observed in gingival (gum) tissues in people with periodontal disease compared with healthy controls.[129] CoQ10 supplementation is therefore commonly suggested for periodontal disease.

Most research in this area has focussed on topical, gingival, application of CoQ10. Only four small clinical studies with between eight and 22 patients have been conducted with oral CoQ10, all but one were open-label, uncontrolled trials.[130,131,132] All studies found significant improvements in some parameters (periodontal score, gingival index, pocket depth, inflammation and bacterial composition of the pocket fluid), but not plaque size/score. Where reported, dosages were 90–100 mg per day for 1–6 months.

Whilst the evidence is not as strong as one would hope, it is promising and, due to the fact that CoQ10 is safe and has many other benefits, supplementation with at least 100 mg per day would be worth considering for this indication.

Review
Coenzyme Q10: A Review of Clinical Use and Efficacy

Polycystic ovarian syndrome

Whilst generally considered a gynaecological condition, an important underlying cause of PCOS is thought to be insulin resistance. Women with PCOS have a higher risk of developing T2DM than women without PCOS, and they may also be at increased risk of CVD.[133]

A double-blind, placebo-controlled trial of 60 women with PCOS found that 100 mg CoQ10, alongside standard treatment with metformin, improved glycaemic control and total and LDL cholesterol, but not other blood lipids.[134] In another double-blind, placebo-controlled trial, CoQ10, 200 mg per day for 8 weeks, was also shown to significantly improve biomarkers for inflammation and endothelial function in women with PCOS.[43]

Another double-blind, placebo-controlled study found that CoQ10, 200 mg per day for 8 weeks, improved glycaemic control and testosterone levels.[135] The same study showed more improvements when CoQ10 was combined with vitamin E, 400 IU per day, in terms of glycaemic control, hormone levels and lipid profiles.[135,136]

Infertility is a common issue in PCOS, and CoQ10, 180 mg per day, has been shown to be effective in improving fertility alongside the fertility drug clomiphene in women with PCOS who did not respond to clomiphene alone.[137]

Based on the above studies, CoQ10 at a dose of 200 mg per day for at least 8 weeks appears to be promising in supporting women with PCOS.

Statin-induced myopathy

Statins are cholesterol-lowering drugs, and have become a cornerstone of CVD prevention. Statin-associated muscle disorders are a common side-effect, affecting 7–29% of patients on statins, and often necessitate drug discontinuation.[138] Statins reduce CoQ10 levels[139] as they block the mevalonate pathway through which we produce CoQ10.[140] As such, CoQ10 supplementation appears logical, especially knowing its importance to the heart muscle.

Interestingly, therefore, the most recent meta-analysis of seven double-blind studies of CoQ10 in statin-induced muscle pain found no benefit.[138] Another meta-analysis of 12 RCTs on the other hand found a significant benefit of CoQ10 for muscle pain, weakness, tiredness and cramps, although not plasma creatine kinase (a marker of heart and/or skeletal muscle damage).[141] Dosages used in the studies included in the above meta-analyses ranged from 100 to 600 mg per day for 1–3 months. Overall, conclusions drawn from reviews are contradictory, with some suggesting a benefit[142] whilst others do not.[140]

An earlier small open-label, uncontrolled trial of 28 patients with statin-induced myopathy found that CoQ10, 60 mg per day, significantly reduced muscle pain (by 54%) and weakness (by 44%) after 6 months of supplementation, although no statistically significant improvement was seen at 3 months,[143] raising the question as to the length of treatment necessary to see results.

It should be stressed that research has focussed on the treatment, rather than prevention, of statin-induced myopathies and that there is no evidence from adequate clinical trials whether CoQ10 may be beneficial for prevention, as theoretical considerations would suggest it is.

Due to the fact that patients on statins are considered to be at risk of CVD and often also have other cardiovascular risk factors and co-morbidities for which CoQ10 has been shown to be of benefit, supplementing CoQ10 alongside statins appears to be prudent at a dose dependent on individual risks and co-morbidities.

Safety

Oral CoQ10 supplements are generally well tolerated and no serious adverse effects have been reported in clinical trials. Gastrointestinal side-effects, such as appetite suppression, diarrhoea, epigastric discomfort, heartburn, nausea and vomiting, have been reported in less than 1% of patients.[144]

Dosages of up to 1200 mg per day in adults and up to 10 mg/kg per day in children appear to be safe, and higher dosages have been used for some conditions.[2]

Drug interactions/cautions

No information on drug interactions has been published. The following potential concerns are of a theoretical nature.

Alkylating agents (types of cancer chemotherapy)

These work by inducing oxidative stress; theoretically, the antioxidant effect of CoQ10 could be counterproductive.[145] Although the clinical relevance of this is unclear, due to lack of research in this area, supplementation during cancer chemotherapy may be best avoided.[1]

Blood-pressure-lowering drugs

As CoQ10 appears to reduce blood pressure (see above), theoretically there could be additive effects with anti-hypertensive drugs, leading to blood pressure dropping too low, although in many of the above studies CoQ10 has been used alongside anti-hypertensive drugs.

Warfarin (anticoagulant drug)

CoQ10 is chemically similar to vitamin K, which has a pro-coagulant effect, and may theoretically reduce the effect of warfarin. Cases where CoQ10 has reduced the effectiveness of warfarin have been reported in the literature,[146,147] although a double-blind, placebo-controlled crossover trial of 21 patients on long-term stable warfarin treatment did not show any effects of CoQ10, 100 mg per day for 4 weeks.[148] As a precautionary measure, patients on warfarin should have their warfarin dose monitored more closely if they choose to supplement with CoQ10.

Pregnancy

There is insufficient clinical research to establish the safety of CoQ10 during pregnancy.

One study used CoQ10 100 mg twice per day from week 20 of pregnancy with no apparent safety concerns.[101] However, until further research confirms the safety of CoQ10 during pregnancy, it should only be used on the advice of a suitably qualified practitioner.

Breastfeeding

CoQ10 is a normal constituent of human breastmilk with concentrations varying by country, possibly due to dietary or genetic factors or differences in measurement techniques; ranges reported have varied from 0.27 µg/l to 1.6 mg/l, and one study found no correlation between maternal plasma levels and levels in breastmilk.

No further information is available on the potential effects of supplemental CoQ10 on breastfed babies, or on lactation and breastmilk.

Age limits/minimum age

CoQ10 has been used safely and successfully in children and adolescents from 3 years old in a variety of conditions, including migraines, dilated cardiomyopathy and juvenile fibromyalgia, as discussed above. Dosages used have been in the range of 1–10 mg/kg with durations of up to 9 months.[144]

Conclusion

Although there are some contradictory findings, overall CoQ10 has been shown to be of benefit in a wide range of disorders, with dosages of 100–300 mg, depending on clinical use.

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