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Case Studies in Personalized Nutrition

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Personalized Nutrition and Lifestyle Medicine for Healthcare Practitioners *series*

Angela Walker

Foreword by Lorraine Nicolle

SINGING DRAGON

LONDON AND PHILADELPHIA

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Cognitive Health through Gut–Brain Communication

Practitioner: Miguel Toribio-Mateas

Introduction

This chapter documents the case report of GA, a female client seeking nutrition and lifestyle advice for the management of insomnia, anxiety and low energy with borderline depressive mood, accompanied by bloating and gastrointestinal discomfort. The case aims to illustrate how neurological and cognitive symptoms can be related to the gastrointestinal system and why working upstream from the gut should be considered as a potential clinical strategy for improving cognitive health.

Initial case presentation

GA is a 72-year-old female who has been under the care of a nutrition practitioner for more than seven years, initially seeking support for the dietary management of ulcerative colitis (UC), loss of bone density as a result of steroid treatment for UC, and borderline hypothyroidism. Although these issues will be referred to as we navigate through our

client's individual health trajectory, the focus of this chapter is on cognitive health and on the translatability of various pieces of evidence to the case in a way that practitioners are able to apply in clinical practice. The case study focuses on a six-month period when cognitive health became the focus for the practitioner and client.

The gut microbiome is of particular interest for this case because of GA's history of UC. The microbe population living in the gastrointestinal (GI) tract, traditionally referred to as 'gut flora', and collectively known as 'gut microbiota' or 'gut microbiome' if including the microbes' genes (Marchesi and Ravel, 2015), interacts with GA as a host through a number of pathways, including neural, immune and neuroendocrine. These act as communication channels through which gut microbes cast local as well as systemic effects on the host biology, both in health and disease (Toribio-Mateas, 2018). Inflammatory bowel diseases (IBDs) such as UC and Crohn's disease (CD) are characterized by alterations in normal composition of commensal gut microbiota or dysbiosis, seen as a key contributory factor to the inflammation underlying these conditions (Basso, Câmara and Sales-Campos, 2018; Knox *et al*., 2019; Qiao, Cai and Ran, 2016; Sartor and Wu, 2017). Calprotectin is used as a routine biomarker to assess the extent to which the gut is compromised by inflammatory processes (Hold *et al*., 2014; Nissilä *et al*., 2017; Zhou *et al*. 2018). Dysbiosis is also seen in functional gastrointestinal disorders (FGIDs) such as irritable bowel syndrome (IBS), constipation, dyspepsia and oesophageal disorders, which the new Rome IV criterion defines as disorders of gut–brain interaction (Drossman, 2016; Drossman and Hasler, 2016; Tack and Drossman, 2017). Last but not least, dysbiosis is widely seen as a mediator in the pathogenesis of a number of other conditions. Particularly relevant to this case are metabolic (Buford, 2017; Lau *et al*., 2017; Ma and Li, 2018; Nagpal, Yadav and Marotta, 2014) and cardiovascular diseases (Battson *et al*., 2018a, 2018b).

The client had been working with this practitioner since 2011. In her late 30s and early 40s GA had experienced what she describes as 'gut issues', featuring ongoing loose, watery and frequent bowel movements. She was tested for common causes of her symptoms, such as the presence of *Escherichia coli*, *Campylobacter*, *Shigella* or *Salmonella* (Lääveri *et al*., 2016; Porter *et al*., 2017). Parasitology was negative,

so no treatment was issued at the time – it was very much a case of 'we cannot find anything wrong with you'. For more than ten years she tried to 'manage her gut' by avoiding ultra-processed foods and alcohol, as these would trigger undesirable symptoms that could last for days. In 2011, at age 65, she was finally diagnosed with UC after a severe episode of blood in the stool and being hospitalized for ten days. She was prescribed prednisolone (40 mg/day) as an anti-inflammatory agent and the aminosalicylate mesalamine as suppositories and orally for the management of the rectal bleeding and diarrhoea. Six months after being discharged, she decided she wanted to manage her condition by means of diet and lifestyle. This is when she had her first nutrition appointment with the personalized nutrition practitioner.

The practitioner used the Measure Yourself Medical Outcome Profile (MYMOP) tool to assess GA's primary symptoms. This is shown in Table 7.1. Note that while the concerns rated in the MYMOP are long-standing, the scoring was taken at a consultation six months prior to the recommendations covered below.

Table 7.1 Pre-intervention MYMOP questionnaire for GA

Concern	Rating	Makes difficult or prevents
Anxiety	0 1 2 3 4 5 ⑥	Makes day-to-day life difficult
Fatigue	0 1 2 3 4 5 ⑥	Shopping, house chores
Sleep	0 1 2 3 4 5 ⑥	Makes day-to-day life difficult
General feeling of wellbeing	0 1 2 3 4 ⑤ 6	

The MYMOP questionnaire was created by general practitioner Dr Charlotte Paterson in the mid-1990s (Paterson, 1996) and was then developed and validated by a research team at the University of Bristol (UK) to be used in any clinical settings where a client presents with symptoms, which can be physical, emotional or social (Paterson, 2004; Paterson and Britten, 2000). It allows the client to rate their own choice of symptoms using a seven-point scale where 0 is 'as good as it could be' and 6 is 'as bad as it could be'. Clients can also rate their general feeling

of wellbeing, and any activities that the symptoms prevent the client from doing.

Looking at the body through a wide-angle lens

While GA has a generally positive outlook on life, she is prone to worry. In recent years this trait has been intensified by having to deal with a difficult personal situation. Her long-term partner – 79 years old – has metastasized prostate cancer affecting several organs and is also affected by cardiovascular disease. Moreover, she is very close to an older family friend who is terminally ill in a nursing home. Additionally, a few months ago, she was physically attacked while taking money out of an ATM, which severely affected her confidence. All of these situations are seen to have contributed to a great degree of the anxiety and borderline depression experienced by the client.

Diet and nutraceutical history

Shortly after the UC diagnosis, GA had started following the specific carbohydrate diet (SCD), and she had adhered strictly to the principles of no grains, sugars (except for honey), processed foods or milk. The SCD purports decreased intestinal inflammation by restoring the balance of bacteria within the bowels and resolving the associated dysbiosis found in IBD (Suskind *et al.*, 2016). Because of her fear of food triggering UC symptoms, her diet had become restrictive and repetitive and mostly based on the following:

- Vegetables: Onions, butternut squash, broccoli, cabbage, spinach, frozen peas, watercress, tomatoes, mushrooms, peppers.
- Fruit: Blueberries, raspberries, bananas, apple, apricot puree, grapes.
- Meat and fish: chicken, tuna.
- Fats: olive oil.
- Nuts: Walnuts.

The client was aware of this and, in order to mitigate potential nutrient deficiencies, she had experimented with a variety of supplements. In the

following summary, 'current' corresponds to the time the MYMOP in Table 7.1 was completed.

- A range of practitioner-grade multivitamin-type products. Currently taking a good-quality multivitamin and mineral complex with added botanicals including green tea extract, curcumin and other nutrients such as lutein and resveratrol.
- Iron, various forms including ferrous bisglycinate, from 5 mg to 50 mg a day. Currently taking 7.5 mg/day food-state iron in addition to 4 mg ferrous bisglycinate in the multivitamin.
- Zinc, also various forms, from citrate to bisglycinate, from 10 mg to 30 mg/day. Currently taking 20 mg zinc as bisglycinate as part of the multivitamin complex.
- A range of probiotic products, from single strain to multi-strain. Currently not taking any.
- Pepsin, betaine and digestive enzymes. Currently not taking any.

Antecedents, triggers and mediators

GA had presented with high levels of low-density lipoprotein cholesterol (LDL-C) for some time before the UC diagnosis. By itself this would normally not be a red flag, but she also had a family history of cardiovascular and neurodegenerative disease. The client's mother had hypertension and her maternal grandmother had developed late-onset Alzheimer's disease (LOAD) in her 80s and she herself carries one copy of the apolipoprotein E (APOE) ε4 allele (see Table 7.2). A practitioner with a good all-round view of a client's condition would look through a wide-angle lens and see her gastrointestinal issues in context, taking into account that dysbiosis of gut microbiota is seen not only in gastrointestinal disorders, as discussed previously, but also in clients with stroke and transient ischaemic attack (TIA). Pre-clinical evidence documenting this relationship has been available for some time (Bu and Wang, 2018; Richards *et al*., 2017), and recent clinical data confirms it (Awoyemi *et al*., 2018; Yin *et al*., 2015).

Additionally, focusing on the client's family history of neurodegenerative disease, a systems-oriented practitioner would also wonder about chronically raised calprotectin and its links with cognitive

impairment. Calprotectin is a heterodimer formed by pro-inflammatory proteins S100A8 and S100A9. Both neutrophils and monocytes are first-line immune defence cells and contain huge amounts of the S100A8/A9 in their cytoplasm. They are recruited to sites of inflammation during infection or sterile injury. Besides its role as a clinically relevant biomarker to monitor disease activity in chronic inflammatory disorders including IBDs and rheumatoid arthritis, extracellular calprotectin interacts with the pattern recognition receptors toll-like receptor 4 (TLR4) and receptor for advanced glycation end products (RAGE) promoting cell activation and recruitment (Pruenster *et al*., 2016). Most relevantly for GA's case, it has been established as a biomarker for the diagnosis and progression of Alzheimer's disease (AD) and dementia (Horvath *et al*., 2016; Wang *et al*., 2018).

The client also reports having had cellulitis of the legs at age 72, having had antibiotics for this condition also at 65 and 66 years of age. The antibiotic prescribed was amoxicillin, 200 mg TID. Pre-clinical data suggests that antibiotic-induced dysbiosis may lead to severe damage of the enteric nervous system (ENS) and how, in animal models, this is coupled with potential long-lasting dysregulation of the microbiota–gut–brain axis, the main line of communication between the gut and the brain (Caputi *et al*., 2017; Stefano, Samuel and Kream, 2017). The additional potential disruption to the gut ecosystem following the antibiotic treatment, alongside existing disruptions characteristic of UC, should be taken into account when evaluating this case through a wide-angle lens.

Investigations

During the seven years the practitioner had worked with GA, a number of tests had been ordered by the practitioner or her medical practitioner. The most relevant investigations are summarized in Tables 7.2, 7.3 and 7.4, with some context. Tables 7.3 and 7.4 include results from as early as 2011 and up to as recently as six months before the case study was written. The aim is to provide an overview of the markers assessed as part of the management of the long-standing issues affecting the patient.

Table 7.2 Genetic testing/genotyping

Gene	Rationale	Result	Significance
APOE	Family history of cardiovascular disease (CVD) and neurodegenerative disease	APOE3/4 genotype, i.e. carries one copy of the APOE-ε4 allele	Increased risk of CVD and Alzheimer's disease (AD)/ dementia
FTO	Family history of neurodegenerative disease	AA genotype for rs6499640, a set of variants for the FTO gene including gene variations in FTO rs6499640, FTO rs8044769 and FTO rs9939609	Increased risk of AD/ dementia
MTHFR	Family history of CVD and neurodegenerative disease, in addition to clinical presentation with anxiety and low mood	GT genotype for rs1801131 (MTHFR A1298C) and AG genotype for rs1801133 (MTHFR C677T)	Reduced MTHFR enzyme activity, compared with people with other genotypes
Cat-echol-O-meth-yltransferase (COMT)	Clinical presentation with anxiety, low mood	AG genotype for rs4680 (COMT V158M)	Reduced activity of COMT activity, leading to slightly higher levels of brain dopamine compared with people with other genotypes

Table 7.3 Functional blood biochemistry and saliva testing

Marker	Rationale	Result	Significance
Homocysteine	Family history of CVD and neurodegenerative disease, in addition to clinical presentation with anxiety and low mood	Several samples, never higher than 9 mmol/L 10 mmol/L would be a cause of concern in this client	Homocysteine levels within an optimal range confirm the need to pay attention to the clinical presentation and not just look for potentially deranged biochemistry
LDL cholesterol	Family history of CVD and neurodegenerative disease	Several samples ranging from 3.9 mmol/L at its highest to 3 mmol/L at its lowest, with a trend to be over 3.5 mmol/L	High LDL would not be significant or clinically actionable as a standalone marker, but with the APOE3/4 genotype, family history of neurodegeneration and concerning symptoms of mild cognitive impairment, it is a marker worth tackling
Four-point salivary cortisol and DHEA in saliva	Lethargy, fatigue, low mood	Assessed twice, in 2011 and 2017 Both samples showed low DHEA:Cortisol ratio, and the December 2017 sample showed cortisol high at the four sample points of the day, with evening cortisol significantly above optimum ranges (1.88 nmol/L, where the optimum range is up to 0.94 nmol/L)	Results are clear signs of autonomic dysregulation Given the similarities between samples, it is safe to say that the autonomic nervous system has been under chronic stress for quite some time See Chapter 3 for further discussion on this test

cont.

Marker	Rationale	Result	Significance
Thyroid function	Lethargy, fatigue, low mood	Based on several samples: free T4 rarely over 15 pmol/L (12.0–22.0 pmol/L) Free T3 mostly below 4 pmol/L (3.1–6.8 pmol/L)	This is one of the issues the client had sought professional support for originally

Table 7.4 Gastrointestinal assessment

Marker	Rationale	Result	Significance
Microbial diversity	Presence of ongoing GI symptoms	Several samples confirming low microbial association compared with a healthy cohort	Low microbial diversity has been associated with a number of conditions, including CVD and neurodegenerative diseases (Toribio-Mateas, 2018)
Faecal calprotectin	Localized inflammation of the GI	Several samples ranging from 102 mcg/L at its lowest to 144 mcg/L at its highest	Aside from GI inflammation (over 50 mcg/L it warrants further investigation and over 120 mcg/L confirms IBD), it shows intestinal permeability affecting gut–brain communication (Kelly *et al*., 2015; Liu and Zhu, 2018; Maes, Kubera and Leunis, 2008; Obrenovich, 2018)

Eosinophil protein X (EPX)	Ongoing GI inflammation and discomfort	Measured twice, at 5.7 mcg/g both times Optimal range is ≤ 4.6 mcg/g	Indicates increased intraluminal release of eosinophil granule proteins, i.e. immune activation in the intestinal lumen, and typically a sign of subclinical inflammation (Peterson *et al.*, 2016)
Pancreatic elastase 1	Bloating, slow digestion	Tested several times, ranging from 234 mcg/g at its highest to 134 mcg/g at its lowest Optimal range is > 200 mcg/g	Identifies mild exocrine pancreatic insufficiency (Domínguez-Muñoz *et al.*, 2017)
Parasitology	Lethargy, fatigue, low mood	No parasites, yeast or pathogenic bacteria have ever been found in any of the samples	It can often be the case that clients with low energy have parasitic microorganisms in their gut, but that wasn't the case for GA

Interpretation

The practitioner decided to focus on the gut as the gateway system for the interpretation of the case, followed by consideration of some key genetic variants. An explanation is provided for of each of the factors considered when 'connecting the dots' of this case.

Microbial diversity

Microbial diversity was a key focus for the practitioner. Why? Because there is evidence that gut microbiota profiles in individuals suffering from low mood and depression show narrowing in microbial diversity (Dinan and Cryan, 2015), rendering the host more susceptible to infection and consequently negatively affecting innate immune function (Patterson *et al*., 2014). The client's microbial composition was assessed by 16S sequencing stool test several times in the last seven years, and microbial (alpha) diversity association was consistently low compared with healthy cohorts, as provided by the testing laboratory (see Chapter 3). Additionally, recent studies have identified that subject biological age correlates with a decrease in stool microbial diversity (Maffei *et al*., 2017) – that is, pathological ageing is associated with a narrowing in microbial diversity whereas healthy ageing correlates with a more diverse microbiota (Dinan and Cryan, 2017). Additionally, GA's dietary pattern had been limited to a few foods that she repeated constantly for years as she was fearful that stepping out of that 'comfort zone' would trigger UC symptoms. Results from a recent open-platform citizen science microbiome research project known as the 'American Gut' project (McDonald *et al*., 2018) found emergent positive associations among the microbiome, metabolome (the collection of metabolites resulting from the interaction between the gut microbiota's genes and that of its host) and the diversity of plant-based foods consumed by participants. Based on more than 10,000 food frequency questionnaires, researchers concluded those people consuming a minimum of 30 different polyphenol-rich plant-based foods per week had the highest microbial diversity.

The significance of chronically raised faecal calprotectin

Faecal calprotectin (FC) is an established inflammatory marker used to assess the presence and severity of IBDs (Argollo *et al*., 2017). Given its high sensitivity as a marker of inflammation in CD and UC, a negative result can safely spare most individuals with idiopathic gastrointestinal symptoms, as well as those with IBS, from having to undergo invasive investigations such as colonoscopies (Waugh *et al*., 2013). Other markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) – both in serum – can provide additional clues to differentiate between IBD and IBS. FC levels correlate significantly with endoscopic disease activity in IBD and are useful in clinical practice for assessment of disease activity and/or remission (D'Haens *et al*., 2012). Additionally, literature on FC agrees that results have good reproducibility (Mumolo *et al*., 2018), and therefore clinicians can trust them to mean the same thing across the board.

Aside from its relevance as a marker in management of gastrointestinal health, so far emerging evidence suggests that FC could also be useful in the assessment of cognitive decline. A study on 22 Alzheimer's patients found almost three-quarters of AD patients presented with faecal calprotectin concentrations higher than normal (>50 mg/kg) (Leblhuber *et al*., 2015). This is interpreted to be a sign of gastrointestinal permeability contributing to inflammation and neuroinflammation as well as affecting availability of key cognitive amino acids such as tryptophan.

APOE genotyping

Practitioners often have high expectations of genetic testing as a tool to help them accurately predict the optimal diets or risk of common diseases for their patients. The reality is that genetic data can only provide partial answers to complex health questions, like providing some of the missing pieces in a large jigsaw that is difficult to complete (Toribio-Mateas and Spector, 2017). What genetic data can provide a really useful insight into, however, is disease risk reduction, prevention and disease management, particularly when other markers that are involved in the development of a condition are assessed – for example, APOE and cholesterol levels, so that the practitioner knows whether the susceptibility conferred by the existence of the gene variant may be

materializing functionally. GA's grandmother had developed late-onset Alzheimer's disease (LOAD). With that in mind and given her signs of cognitive impairment, GA's medical practitioner recommended APOE genotyping.

The human APOE gene exists in three common allelic variations: ε2, ε3 (the wild type) and ε4 (Myers *et al*., 1996). There are six possible genotypic combinations, including three homozygous (ε2/ε2, ε3/ε3 and ε4/ε4) and three heterozygous (ε2/ε3, ε3/ε4 and ε2/ε4). The ε4 allele, resulting in the ApoE4 protein, has been shown to be associated with genetic risk factors for developing LOAD: ε4 heterozygotes are at 2–3 times more risk, and ε4 homozygotes have up to 12 times more risk than those with ε3 wildtype alleles (Kim, Basak and Holtzman, 2009). Furthermore, this genotype has been shown to be associated also with general cognitive decline in cognitively normal individuals with no symptoms of AD-related disorders (Caselli *et al*., 2011, 2009). Only around 40% of individuals who develop LOAD possess an ε4 allele. For practitioners working with genetic data, this means that a ε4 variant can only provide susceptibility estimates of the likelihood of developing LOAD – that is, carrying the ε4 allele means greater risk (Farrer *et al*., 1997; Ungar, Altmann and Greicius, 2014) but it doesn't necessarily guarantee that a person will develop the condition.

The catechol-O-methyltransferase gene: COMT

GA is – to a certain extent – a pathological worrier who fears uncertainty, particularly when it comes to how food might affect her bowel. However, taking into consideration the fact that the severity of her UC resulted in her being hospitalized, it is easy to see how her anxiety could be somewhat justified.

The COMT gene provides instructions for making an enzyme called catechol-O-methyltransferase which is particularly important in an area at the front of the brain called the prefrontal cortex, a region that is involved with personality, planning, inhibition of behaviours, abstract thinking, emotion and short-term (working) memory. To function efficiently, the prefrontal cortex requires dopamine and noradrenaline, and catechol-O-methyltransferase helps break these down so that they are present in adequate amounts. When this enzyme is hyperactivated,

dopamine – responsible for drive or 'get up and go' – is disposed of too quickly, leaving a person feeling flat and potentially apathetic. Conversely, when activity of catechol-O-methyltransferase is reduced, higher levels of dopamine remain in the prefrontal cortex. In the shorter run, this can have a positive effect on the experience of reward (Wichers *et al*., 2008), as well as verbal fluency and creativity (Zhang, Zhang and Zhang, 2014). In the longer run, the impaired ability to break down these catecholamines can result in higher risk of impulsivity, neuroticism and anxiety disorders (Gottschalk and Domschke, 2017; Soeiro-De-Souza *et al*., 2013; Stein *et al*., 2005).

Methylenetetrahydrofolate reductase (MTHFR) and anxiety

The 5,10-methylenetetrahydrofolate reductase (MTHFR) gene is responsible for the metabolism of folate. There is evidence of common polymorphisms in this gene, including MTHFR C677T and A1298C, and their association with anxiety disorders (Gilbody, Lewis and Lightfoot, 2007) as well as depression (Zintzaras, 2006). It is worth noting that not everyone who has these type of genetic variants presents with low folate or high homocysteine. Indeed, that is GA's case, whose bloods over the five years prior to writing this report never showed low folate or high homocysteine. (This is despite her having an even greater susceptibility due to the presence of a variant in another gene – the NBPF3 gene – which is associated with lower circulating levels of pyridoxine – vitamin B6.) The point highlighted here is that folate and vitamins B12 and B6 are part of the methyl donor subgroup of B vitamins (Sharma and Litonjua, 2014; Tanaka *et al*., 2009). Even though these three markers were within normal levels in blood tests, the practitioner felt that sensible supplementation was warranted, due to the presence of her genetic variants and her clinical presentation of extreme fatigue and low mood. This will be discussed further in the next section.

Recommendations: Tackling a complex system

The practitioner agreed with GA that the focus should be on lifestyle and food, with only a few selected nutraceuticals that merited their use

based on clinical evidence and previous experience of effectiveness in similar cases. The following sections detail the recommendations for each of the connected areas tackled as part of this case.

Stress and sleep

Gut sensitivity and motility had been a chronic feature in the client's life, as has the dysregulation of autonomic nervous function and the hypothalamic–pituitary axis through lack of cortisol homeostasis. Emotions such as stress play a substantial role in cognitive health (Wingenfeld and Otte, 2018) and are capable of disrupting brain–gut homeostasis (Pellissier and Bonaz, 2017). Recent evidence points to oncologic caregivers, both formal and informal (i.e. a paid carer or someone caring for their partner at home), presenting with higher overall perceived stress levels (including high anxiety, and higher perceived self-reported psychological stress rate) compared with caregivers of geriatric patients with chronic diseases (Aguiló *et al*., 2018). GA cares for both a patient with cancer (her long-term partner) and an older friend in her 90s. When asked to rate her own stress levels by MYMOP, she rated them as 6 or 'as bad as they could be'. Her MYMOP score for sleep was also 6. She told her practitioner that she was getting a maximum of three hours' uninterrupted sleep per night and feeling exhausted in the morning. Chronic stress is known to contribute to the dysregulation of the hypothalamic–pituitary–adrenal system and to have a negative impact on sleep quality, which in the longer run has been seen to lead to sleep disturbance and depression as well as decreased brain-derived neurotrophic factor (BDNF) levels (Giese *et al*., 2013; Schmitt, Holsboer-Trachsler and Eckert, 2016). BDNF belongs to a family of small secreted proteins with very well-researched positive effect on hippocampal synaptic plasticity, through which it promotes learning and memory, and enables resilience to exposure to glucocorticoids such as cortisol –that is, endurance to psychological stress (Leal, Bramham and Duarte, 2017).

Sleep disturbances and disorders have also been implicated in cardiovascular morbidity and mortality (Hall, Brindle and Buysse, 2018), and GA has a family history of CVD and carries some risk factor – both genetic (MTHFR and APOE polymorphisms) and biochemical (elevated LDL)

– which make a cardiovascular event a more tangible possibility, so it was decided to tackle the client's 'broken system' from the sleep angle first. To do that, the practitioner agreed with GA the introduction of anxiolytic botanicals with a long history of traditional use.

Bacopa monnieri and Gotu kola

In a randomized, double-blind, placebo-controlled clinical trial with a placebo run-in of six weeks and a treatment period of 12 weeks in patients of an average age of 73 years, 300 mg/day standardized *Bacopa monnieri* extract helped relieve anxiety and symptoms of depression (Calabrese *et al*., 2008). The same dose had previously been shown to improve cognitive functions such as learning and memory in healthy participants compared with placebo (Stough *et al*., 2001). More recent studies have supplemented *Bacopa* at slightly higher doses with positive effects on cognitive performance and anxiety (Sathyanarayanan *et al*., 2013). *Bacopa monnieri* is a shrub used traditionally in Ayurveda for the balancing properties of its terpenoids, known as bacosides, which have been seen to lead to enhanced BDNF production and subsequent improvements in neuroplasticity (Sangiovanni *et al*., 2017). In this practitioner's clinical experience it helps with sleep quality and reduction of anxiety in a 2–3-week time frame. Furthermore, *Bacopa monnieri* can work synergistically with Gotu kola (*Centella asiatica*), also known to attenuate anxiety and improve cognition (Jana *et al*., 2010) as well as modulate mood (Wattanathorn *et al*., 2008). In pre-clinical models, terpenoids in Gotu kola have been seen to increase hippocampal synaptic density and to improve memory and executive function.

Introducing Mediterranean diversity

Perhaps the most important recommendation of all was asking GA to focus on including a diversity of brightly coloured vegetables and fruit as part of her daily diet and to try not to repeat the same vegetables every day, but to rotate them. The rationale was to emulate the beneficial effect of dietary diversity seen in the Mediterranean diet (MD) on the gut microbiota.

Why is diet diversity so important? There is plenty of evidence pointing that way. For example, a recent study of 31 Spanish adults in

the north of Spain found that participants with the closest adherence to a Mediterranean-style dietary pattern to be the most statistically significant and beneficial changes in a number of bacterial communities including overall higher abundance of *Bacteroidetes*, *Prevotellacea* and *Prevotella*, and a lower concentration of *Firmicutes* and *Lachnospiraceae*, all of which been found to display anti-inflammatory properties (Gutiérrez-Díaz *et al*., 2016). The alterations in gut microbiota richness and spread triggered by the MD are consistent with previously reported clinical data on the effects of increased dietary fibre from vegetables, legumes and whole grains – meaning minimally processed – as well as phenolic compounds and carotenoids typically featured in MD foods such as seasonal and citrus fruits, leafy, pod and root vegetables, in addition to bulbs, such as onions, garlic, leeks, as well as red wine and coffee (González *et al*., 2014; Tap *et al*., 2015).

The same research team (2016) reported a link between the high diversity of dietary bioactive compounds in the MD and higher levels of a commensal bacteria group known as *Clostridium* cluster XVIa, particularly *Faecalibacterium prausnitzii*. This bundle of Firmicutes is known for their ability to colonize the mucin layer of the human colon, thereby aiding in the maintenance of gut homeostasis (Lopetuso *et al*., 2013). It includes species such as *Eubacterium rectale*, *Papillibacter cinnamivorans*, *Eubacterium ventriosum*, *Butyrivibrio crossotus*, *Clostridium orbiscindens*, *Coprococcus eutactus*, *Roseburia intestinalis* and *Faecalibacterium prausnitzii* known to plays a major role in mediating the production of butyrate from fermentable dietary carbohydrates (El Aidy *et al*., 2013; Van den Abbeele *et al*., 2013). F. prausnitzii is considered to have strong anti-inflammatory properties (Lopez-Siles *et al*., 2017). This is largely mediated by its ability to produce butyrate, thereby protecting the gut mucosa (Sokol *et al*. 2009), and for its ability to block pro-inflammatory cytokines such as NF-kappaB and IL-8 production (Sokol *et al*., 2008). Low levels of F. prausnitzii, have been associated with a peripheral inflammatory state in patients with cognitive impairment and brain amyloidosis (Cattaneo *et al*., 2017). Low levels of genus *Roseburia* microbes have been seen in patients with UC (Bajer *et al*., 2017; Machiels *et al*., 2014), as well as in those affected by constipation-predominant irritable bowel syndrome (C-IBS) (Gobert *et al*., 2016). Figure 7.1 depicts the impact of dietary diversity on the gut–

brain axis. It is worth noting that the microbial ecosystem in the gut is extremely complex; individual microbes that are part of a group or family can sometimes be found to have effects that contradict those of the group they belong to. For example, *F. prausnitzii* or *Roseburia* are part of the Firmicutes phyla, but tend to behave differently compared with other Firmicutes.

Because of GA's attachment to the principles of the specific carbohydrate diet, she had been limiting the vegetables and fruit she consumed for years. Although there are anecdotal reports of benefit from this and other types of diets in IBD, there is no consistent clinical data to support their effectiveness as long-term dietary patterns. On that basis, the practitioner suggested to introduce new colours of the same vegetable as a first step forward – for example, red, white and green cabbage, green, red, yellow and orange peppers, different types of mushrooms, from oyster to shiitake, maitake, button, chestnut – increasing diversity by mindfully adding five or six portions (about 80 g each) of vegetables daily in total, with a new vegetable or a different colour of the same vegetable every couple of days.

Although the emerging evidence on the effects of dietary diversity on the microbiome and the human host has been focusing on plant-based foods, the practitioner believes there is also argument for protein diversity. Different meats and types of fish provide different amino acid profiles along with minerals and trace elements. Based on that principle, the client was asked to include a variety of good-quality meat cuts, organic if possible, and of wild-caught fish such as Alaskan salmon, mackerel, cod, coley or pollock, as well as tinned sardines, ideally in olive oil. In fact, as a clinician looking at GA's individual case through a wider-angle lens, the practitioner emphasized the role of olive oil as a simple yet extremely powerful food-based intervention that targets both the gut and the cardiovascular system. To illustrate this point, recent clinical evidence described how adding a mere 25 ml/day of olive oil infused with fresh thyme has been seen to improve the lipid profile of hypercholesterolemic individuals, and the cardioprotective effect is believed to be mediated by an increase in *Bifidobacteria* triggered by the phenolic compounds found in olive oil and thyme, both food items typically featured in Mediterranean dietary patterns (Martín-Peláez *et al*., 2017).

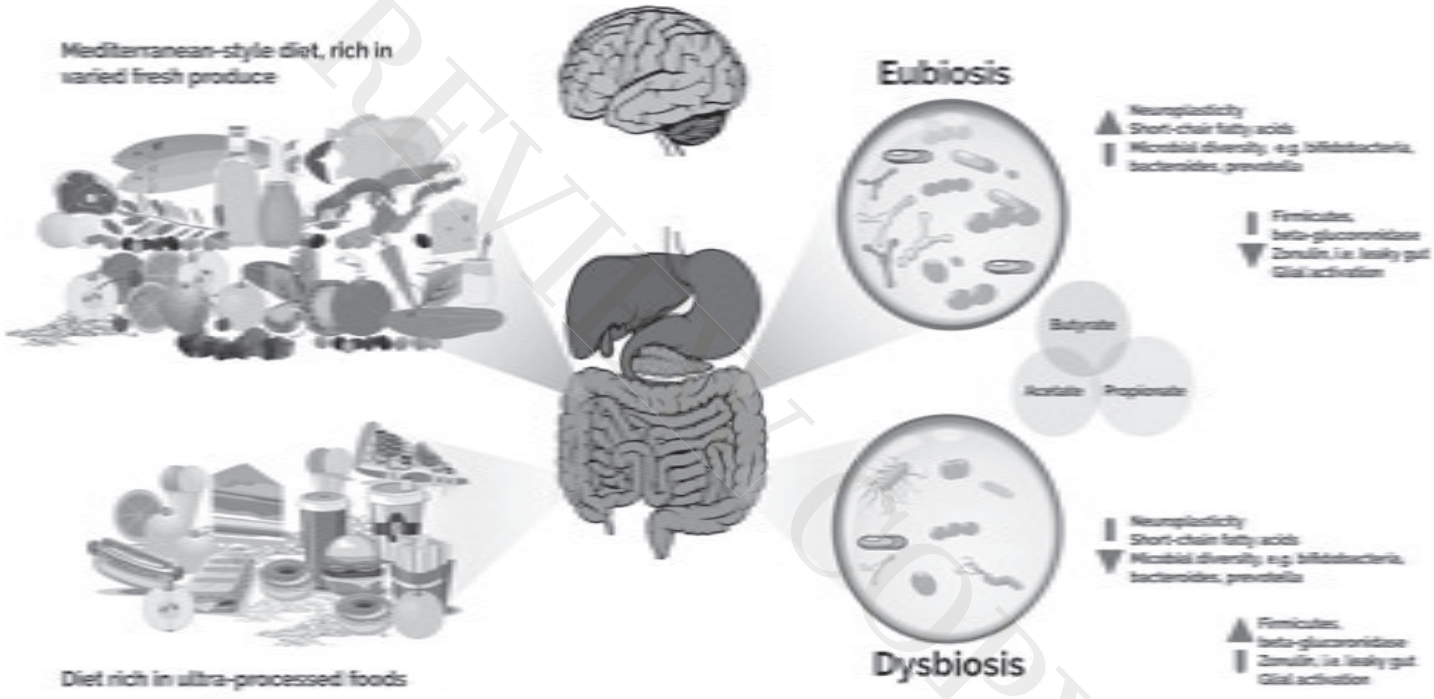

Figure 7.1 Dietary diversity and its effect on the gut–brain axis (see colour plate)
Source: Reproduced with permission from Toribio-Mateas (2018)

Red rice yeast

GA's medical practitioner had been keen for her to take statins in order to manage her LDL cholesterol levels, but GA had wanted to tackle this issue by means of nutrition and lifestyle. Because of the increased predisposition to cardiovascular and cerebrovascular events, the practitioner suggested a three-month course of red rice yeast, 400 mg/day, providing 1.6 mg monacolin K, a natural substance chemically identical to lovastatin, that has been recognized as responsible for its cholesterol-reducing properties (Nguyen, Karl and Santini, 2017). In the same way as lovastatin and other statins, monacolin K inhibits hydroxymethylglutaryl-coenzyme A (HMG CoA) reductase, the rate-limiting step in cholesterol synthesis, which also depletes coenzyme Q_{10} (CoQ_{10}) levels from the body. On that basis, and following recent clinical evidence of CoQ_{10} administration alongside red rice yeast (Mazza *et al*., 2018), a supplement that contained 20 mg CoQ_{10} was recommended.

While red rice yeast works on exactly the same pathway as statins, in the author's clinical experience it is the very low dose of the 'natural statin' in red rice yeast that seems to enable the beneficial effects on LDL cholesterol reduction, but without the side effects experienced by those on lovastatin and other statins, such as muscle pain.

Fermented foods

Fermented foods provide a way to re-establish gut microbiota homeostasis that has been reported to be a relevant strategy to prevent or attenuate several conditions, not just gastrointestinal but also cardiovascular and metabolic disorders (Pimenta *et al*., 2018). Given the practitioner's own clinical experience over the last few years, he was particularly keen on the use of kefir, a complex fermented dairy product created through the symbiotic fermentation of milk or sucrose-enriched water by lactic acid bacteria and yeasts contained within an exopolysaccharide and protein complex called a kefir grain (Bourrie, Willing and Cotter, 2016). Kefir is an excellent source of microbial diversity, providing up to 60 different species, including *Lactobacillus casei/paracasei*, *Lactobacillus harbinensis*, *Lactobacillus hilgardii*, *Bifidobacterium psychraerophilum/crudilactis*, *Saccharomyces cerevisiae* and *Dekkera bruxellensis* (Laureys and De Vuyst, 2014). Regular consumption of kefir and its exopolysaccharides has been

associated with improved digestion and tolerance to lactose, as well as with antibacterial and hypocholesterolaemic effects, control of plasma glucose, antihypertensive effect, anti-inflammatory effect, antioxidant activity, anti-carcinogenic activity, anti-allergenic activity and healing effects (Lim *et al*., 2017; Rosa *et al*., 2017).

Kombucha, a fermented drink made from sugared black tea by a symbiotic colony of bacteria and yeast (SCOBY), is a natural source of short-chain fatty acids, enzymes and living microbes that has been seen to inhibit pathogenic bacteria such as *Escherichia coli*, *Vibrio cholerae*, *Shigella flexneri* and *Salmonella typhimurium* (Bhattacharya *et al*., 2016).

GA was provided with instructions on how to make water kefir and kombucha at home and she was advised to drink up to two glasses (600 ml) of water kefir and one glass (300 ml) of kombucha daily. The practitioner suggested to start with 50 ml on day one and to build up by an additional 50 ml a day until reaching the suggested dose. Based on his own clinical experience, this gentle approach to introducing fermented foods works well with individuals with gut issues whose GI tract may be 'shocked' by the high amounts of live bacteria contained in kefir and kombucha, experiencing bloating and flatulence as a result, which can detract from compliance going forward. Even though these are food sources of probiotic microbes, they are extremely powerful and should be used sensibly. For clarity, the same applies to milk kefir and kefir made with milk substitute (e.g. coconut).

Methylated B vitamins

The idea that methylated B vitamins – for example, methylfolate, methylcobalamine – are superior has quickly spread among nutrition practitioners, particularly for clients like GA whose folate reductase activity is potentially limited by her genetic variants. In fact, the availability of nutrigenetic testing and the lack of precise clinical protocols has led to a variety of treatment strategies that rely on hypotheses and mechanistic studies (Oberg *et al*., 2015), including supplementation with L-methylfolate with or without other B vitamins. Hyperbole aside, what is clear is that folate, folic acid and 5-methyltetrahydrofolate are not the same thing and that those with potentially detrimental MTHFR variants are more likely to benefit from

methylated B-vitamin forms than the corresponding non-methylated versions. In this particular case, L-methylfolate was recommended to support the synthesis of the three major neurochemicals: serotonin, noradrenaline and dopamine – across the blood–brain barrier (Leahy, 2017) which has been seen to achieve significant improvements in self-reported depression symptoms and functioning in naturalistic settings (Shelton *et al*., 2013) – that is, real-world settings like those nutrition practitioners operate in. As discussed previously, the client didn't present with raised homocysteine but reported some of the symptoms typically seen in cases of B-vitamin deficit or under-utilization, including fatigue, 'brain fog' and low mood. L-methylfolate or 5-MTHF also prevents the potential negative effects of unconverted or unmetabolized folic acid in the peripheral circulation (Scaglione and Panzavolta, 2014), which provides another reason for practitioners to consider this form of folate when looking at suitable options for a specific case.

GA has a COMT gene variant that makes her prone to experiencing the negative effects of dopamine recirculation. Why would methylfolate be an appropriate option for this client when this form of folate supports the synthesis of dopamine? The answer, as mentioned earlier, is not to 'treat the SNP' or 'second guess' a reaction based on genetic data or even on genetic data coupled with blood/urine biochemistry. The advice is to try, with the client's consent, assessing progress by means of the collection of patient-reported outcome measures like MYMOP scores. As evidence of the reactions to different types of B-vitamin supplements is scarce and too heterogenous to provide solid support to make a clinical decision (Anderson *et al*., 2016), it is necessary to keep talking to the client to keep them engaged in the process and to find out how they feel appropriate adjustments can be made. Based on client reporting, changes may include increasing/decreasing the dose of the same form of the same nutrient or changing to another form altogether.

In this practitioner's clinical experience, it isn't unusual for individuals with a genetic predisposition to having high homocysteine to present with levels that are within an optimal range. This confirms the need for practitioners to pay attention to the clinical presentation and not issue recommendations based purely on laboratory tests. The methylated B-vitamin supplementation for GA included 200 mcg

calcium L-methylfolate, 1000 mcg methylcobalamine and 20 mg pyridoxal-5-phosphate.

Progress and development

Sleep

After 500 mg Gotu kola and 500 mg *Bacopa monnieri* daily for a month, GA described her sleep as 'the best she's had in years' and rated it as a 2 in the follow-up MYMOP (see Table 7.5). This is an improvement of four points, having been rated 'as bad as it could be' at 6 only four weeks earlier.

Dietary diversity

Introducing diversity can be daunting for someone whose repertoire of foods is limited because of fear of triggering symptoms. Using a tool like the '50 food chart' as shown in Figure 7.2 (Toribio-Mateas, 2018) can be a very useful way for practitioners to assess where the starting point of a particular client is with regard to diversity. For someone who has no issues getting up to 25 or more foods in a week, pushing it a bit harder and introducing different foods altogether is likely to be easy.

For someone who is more limited in their food diversity, using 'baby steps' and introducing the same food in different colours – for example, red, yellow and green peppers, red and white cabbage – is an easy way to increase nutrient density, improving the likelihood of compliance and without overwhelming the client. Being more mindful of the variety of colours in her basket was the advice given to GA, a recommendation that she was able to implement fairly easily over the course of a few weeks, finally reaching close to 50 different foods.

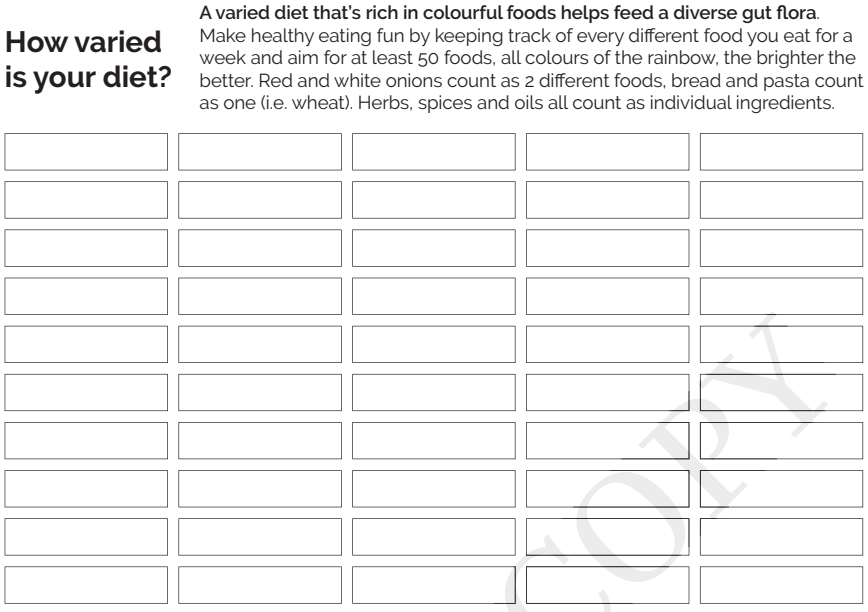

Figure 7.2 The practitioner's '50-food challenge' chart
This an example of a simple but powerful data collection tool used in clinical practice to engage with clients in a light-hearted way so that they report back to their practitioner on their dietary diversity.
Source: Reproduced with permission from Toribio-Mateas (2018)

Red rice yeast

Within three months of supplementation with 400 mg/day, providing 1.6 mg monacolin K and 20 mg/day CoQ_{10}, GA's LDL cholesterol levels had decreased from 3.6 to 3 mmol/L.

Fermented foods

The client really liked the idea of making both water kefir and kombucha at home as part of her 'taking back control of her health'. GA followed the instructions and staged the introduction of both by limiting the amount to 50 ml a day until reaching the recommended two glasses (600 ml) of water kefir and one glass (300 ml) of kombucha every day. She mixed the water kefir and the kombucha and diluted them with filtered water which she drank throughout the day. When asked to described how her gut felt, she said she had had the best bowel motions

since she remembered. No MYMOP score was taken for this, but GA agreed that her gut health had contributed to her general feeling of wellbeing, which had improved from an initial 6 to a follow-up score of 3 (see Table 7.5).

Methylated B vitamins

The client believes these have contributed to her improved energy and her ability to think more clearly. This is reflected in her MYMOP score for energy, which has gone from 6 (as bad as it could be) to 3 (see Table 7.5). The practitioner did not document a MYMOP score for foggy thinking, but GA confirmed that her cognitive function has improved, even if her stressful situation at home was still ongoing. However, a MYMOP score of 3 was recorded for anxiety (see Table 7.5). That is a reduction of three points from the initial rating of 6 four weeks prior to the follow-up. There is some evidence that methylated B vitamins provide relief for depressive and anxiety symptoms and improvement of quality of life in adults with depression (Anderson *et al*., 2016; Fava and Mischoulon, 2009; Lewis *et al*., 2013; Papakostas, Cassiello and Iovieno, 2012).

The improved sleep duration and quality has quite possibly had a knock-on effect on energy. However, the client feels (in her own words) that 'the B vitamins are doing something' and, on that basis, the practitioner recommended ongoing daily supplementation at the same dose for at least another six months. Table 7.5 summarizes the improvements in the MYMOP questionnaire discussed above.

Table 7.5 Post-intervention MYMOP questionnaire for GA

Concern	Rating	Makes difficult or prevents
Anxiety	0 1 2 ③ 4 5 6	Makes day-to-day life difficult
Fatigue	0 1 2 ③ 4 5 6	Shopping, house chores
Sleep	0 1 2 ③ 4 5 6	Makes day-to-day life difficult
General feeling of wellbeing	0 1 2 ③ 4 5 6	

These follow-up scores were taken eight weeks into the dietary and supplement recommendations.

Follow-up testing was not undertaken for the gastrointestinal function markers or salivary cortisol due to cost issues. In the practitioner's experience this highlights the necessity for focusing on clinical presentation and the usefulness of a validated PROM such as MYMOP. Comparison of before and after symptom ratings and the application of critical thinking helps to establish what body systems are implicated in the changes in scoring.

Although it is always reassuring to add data to a patient's clinical file, it may sometimes be not absolutely necessary, particularly when self-reported wellbeing has increased.

Discussion and reflection

This case provides a great example of a clinical scenario where several systems are affected and how this can be both exciting and daunting for a systems-oriented practitioner. The practitioner even chose not to tackle some other less systemic/more localized symptoms reported by the client in order to keep this complexity within manageable parameters. One such symptom was ongoing idiopathic itching, particularly in the back, which seems to be responding well to a diamine oxidase (DAO) supplement to manage histamine breakdown in the gut. For situations where a bioactive compound is difficult to source from food and/or requires a drastic change in dietary habits – for example, a low-histamine diet – practitioners should focus on patient preferences. A low-histamine diet was discussed with GA as a first-line intervention but was seen as too cumbersome by the client who expressed a preference for trying a supplement instead. Methylated B vitamins may also have helped with regard to methylation of histamine.

Why would complexity be daunting, you might wonder. Well, in the author's own experience in clinical education, practitioners can sometimes spend excessive time and resources – both theirs and their clients' – trying to answer the many questions posed by the multiple systems involved in the clinical problem they are up against. As an analogy, when trying to answer a black-or-white-type question – for example, 'Is the client pregnant?' – answers are also either black or white.

This is typical of pathology-related questions where the answer is yes or no, positive or negative – just as you cannot be 'a little pregnant'. The same would apply to being infected by the HIV virus. Answers for these two 'yes/no' clinical questions are either positive or negative. But in systems-biology-based clinical practice, many of the questions do not lend themselves to black/white, yes/no answers. Practitioners tend to operate somewhere between certainty and chaos (Innes, Campion and Griffiths, 2005), making sense of complexity based on a number of partial answers and a range of markers, and marrying those up with their clients' clinical presentation. [Editor's note: See Chapter 2 for a deeper discussion on complexity in clinical practice.]

Tests are just like pieces in a jigsaw. They help the practitioner to get 'the bigger picture' and go deep into a specific area of interest, as needed. For example, in GA's case, a dysfunctional gut microbiota is just one of the many factors contributing to her loss of overall homeostasis. The client's clinical presentation has been chronically characterized by severe gastrointestinal symptoms, which gives the practitioner a way into a broken system that she can relate to. Referring to the prior point on time and resource effectiveness, finding a relatable starting point makes it easier for a systems-oriented practitioner to negotiate how to tackle a case. Biological anthropologists Edes and Crews would see GA's disturbed gut ecosystem as the type of physiological and somatic dysregulation that results from ongoing exposure to 'stressors and senescent processes accumulated over the person's lifespan' (Edes and Crews, 2017, p.44). In other words, her chronic gastrointestinal dysregulation hasn't taken place in isolation. It has simply added to what is referred to in literature as allostatic load, a concept defined by McEwen and Stellar as 'the cost of chronic exposure to fluctuating or heightened neural or neuroendocrine responses resulting from repeated or chronic environmental challenge that an individual reacts to as being particularly stressful' (McEwen and Stellar, 1993, p.2093).

In this particular case, the most tangible manifestation of the excessive allostatic load materialized as extreme anxiety, leading to poor sleep quality and lack of energy, which, in turn, led to her inability to think clearly, or 'foggy thinking', and some memory loss typically seen in mild cognitive impairment. Working on those areas as layers

superimposed on to a core intervention – that is, the gut – has resulted in a satisfactory overall improvement. But GA's case could have been tackled differently, and successfully, by another practitioner using the same systems-oriented approach but getting into the system from another angle. GA's case illustrates how practitioners should always combine their clinical insight and expertise with good-quality scientific evidence and the results of any tests they may choose to use based on that evidence, in order to provide creative solutions that support complex clinical scenarios, thereby helping their clients achieve better health outcomes.

Q&A

AW: I know you are a fan of the Mediterranean diet. We know it has been defined in some of the studies you mention in your case, but there is also a lot of misunderstanding around this. For example, some claim the EatWell Guide (formerly the EatWell Plate) is a version of the Mediterranean diet. Can you explain how you define it for your clients, how you coach and mentor someone to introduce it (over and above the 50 foods, which is one key element)?

MTM: I know there are various different definitions of the Mediterranean diet. I like to think of it as a 'pattern' rather than a 'diet'. As such, it features high sources of dietary fibre with high unsaturated fatty acids relative to saturated fatty acids and is low glycaemic load – that is, it includes foods with lower glycaemic indices that tend to promote favourable insulin responses and postprandial blood glucose profiles, enhancing appropriate appetite regulation. It is also rich in a diversity of dietary polyphenols. The diversity in structure and function of polyphenols could influence a variety of metabolic pathways, such as inhibition of lipogenesis, stimulation of catabolic pathways, reduction of chronic inflammation and upregulation of uncoupling proteins (a measure of healthy mitochondrial function) (Guo *et al*., 2016).

AW: Reflecting on the case, is there anything you would do differently?

MTM: Quite probably. I am a fairly creative practitioner so I am always open to possibilities. However, in my clinical experience, the gut is an 'easy' point of entry into most people's systems. If I was to use just one single intervention out of all the things I did for GA, I would have started with the increase in dietary diversity first and foremost.

AW: Was there any other advice you gave to GA regarding sleep, such as light or temperature, or was it purely the supplements and diet change that improved her sleep so rapidly?

MTM: Yes, I certainly gave her wider recommendations to improve sleep. For me it's about comfortable sleep conditions, including the mattress, the duvet or blankets, but most of all about the light. Particularly where the hypothalamus–pituitary–adrenal (HPA) axis is involved, avoiding exposure to light during the night – for example, a window with no curtains close to a streetlight or lights on during the night. A room that is totally blacked out during sleeping hours is ideal and can make a great contribution to improved sleep quality.

AW: I know you are keen to introduce greater evidence-based practice into personalized nutrition, recognizing that evidence comes from many different sources. I love how you use a combination of sources in this case. What is your advice to a less experienced practitioner on how to develop that clinical insight?

MTM: Start always by looking at the highest sources of evidence – that is, randomized controlled trials (RCTs) and pooled data from systematic reviews or meta-analysis. Failing the availability of those, then look into cohort studies or even single case studies like those in this book. Be mindful of your intervention's likelihood to cause harm. If you are recommending increasing how much broccoli someone eats, you're unlikely to harm them, although this may make a few people more uncomfortable in situations where gut dysbiosis and sulphate-reducing bacteria may lead to an increase in bloating. So even if there was no RCT documenting exactly how to use broccoli in clinical practice, you could be pretty sure you'd be safe. The nastiest thing your client can

experience is flatulence, which will clear after they reduce the amount of broccoli they eat. But when you're recommending individual nutrients, sometimes at high dose, that could potentially lead to issues that you hadn't anticipated. For example, you could argue that *Bacopa* and Gotu kola are natural, and hence safe. However, I would not feel comfortable recommending their use at dosages that are ten times what has been seen to be safe and effective in a clinical trial. If there was no clinical data for either of these botanicals, I would always err on the side of caution and use them as close to a food-type use as possible – for example, as a tea instead of as a high-dosage supplement. The same applies to probiotics. I feel much more comfortable working with food-based ferments than with supplements, although if a certain microbial strain has proven clinical efficacy for a specific condition, I would be only too happy to recommend it too. In general, I would just call for common sense in how we approach nutrition, and for steady use of resources that provide access to good-quality clinical data, such as PubMed or Nutrition Evidence.

BOX 7.1 CLINICAL DATA RESOURCES FOR PERSONALIZED NUTRITION PRACTICE

Nutrition Evidence is a database created to support evidence-based practice in nutrition and lifestyle medicine. It is produced by BANT and it is open access. It can be found at www.nutrition-evidence.com.

Pubmed is available to all – www.ncbi.nlm.nih.gov/pubmed.

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