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Feeding melancholic microbes:

MyNewGut recommendations on diet and mood

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Abstract

Depression is a highly prevalent disorder which exerts a major economic impact in all European countries. The brain-gut-microbiota axis has been described as a new paradigm for advancing understanding and treatment of the disorder. There is now over-whelming evidence to support the fact that gut microbes have a major impact on central neurochemistry and behaviour, especially stress related disorders such as depression. Recent studies indicate that patients with depression have a gut dysbiosis. The reason for this dysbiosis is uncertain. Over recent decades, dietary patterns in Europe and elsewhere have undergone major compositional changes, with increased intakes of red meat, high fat foods, and refined sugars. Individuals who consume a Mediterranean diet have lower rates of depression and a recent study suggests that a Mediterranean diet may have antidepressant properties. Assuming this to be the case, which components of the Mediterranean diet mediate the effects? Highly levels of polyphenols or polyunsaturated fatty acids are obvious candidates. We in the MyNewGut consortium recommend that patients with depression or vulnerability to depression should be encouraged to enhance a plant-based diet with a high content of grains /fibres and fish.

Keywords: MyNewGut, depression, gut microbiota, diet, dysbiosis

Background

Depression is not only the common cold of psychiatric disorders but one of the most prevalent medical conditions. In Europe the economic impact of depression accounts for one third of the cost of all psychiatric and neurological disease (1). While several subtypes of mood disorder have been described the most important in terms of prevalence are major depression (unipolar) and bipolar affective disorder, previously called manic depression. The point prevalence of major depression in Europe is between 3% - 6% and it is clear that no society is immune to the disorder (2). Despite major investment in studies exploring the biology of depression, it remains a syndrome diagnosed by the presence of a cluster of symptoms (3) and not by objective laboratory investigations. Most, though not all cases of depression arise due to negative life events in a setting of psychosocial stress, with genetics and early life adversity frequently yielding vulnerability to the disorder. The core features of depression are low mood and/or anhedonia, the inability to feel enjoyment. Anxiety is often an important feature of major depression, though it can be a distinct disorder, often presenting as generalized anxiety disorder, panic disorder or obsessive compulsive disorder.

Current pharmacotherapy in Europe and elsewhere for treating major depression comprises the manipulation of monoaminerigic systems (catecholaminergic and serotonergic systems). (4). Clinical efficacy of these drugs is limited by a delayed onset of action and a considerable proportion of patients (maybe as high as 40%) who do not respond adequately to treatment (5). Psychological therapies, likewise have limitations, and are used either on their own or in combination with medication. Cognitive behaviour therapy (CBT) and mindfulness are the most

widely used and studied psychological therapies. For many patients a combination of antidepressants and CBT/mindulness is considered as the optimal therapy.

Over the past decade there has been a major focus on the role of inflammation in the pathophysiology of depression and in determining vulnerability to the disorder. It is established that major depression correlates with definite increases in pro-inflammatory cytokines such as inteleukin-1 (IL-1), IL-8 and TNF-alpha (6). These cytokines potently activate the hypothalamic-pituitary-adrenal axis (HPA) and may play a major part in maintaining the HPA over-activation seen in depression(7). Effective treatment of depression by whatever modality is accompanied by suppression of pro-inflammatory cytokines and decreased activation of the HPA. It is of interest from a nutritional perspective that a Mediterranean diet which is viewed as having anti-inflammatory effects is associated with less depression than standard northern European diets (8).

The FP7 EU project MyNewGut (www.mynewgut.eu) is a five-year initiative (2013-2018) integrated by a highly multidisciplinary team that cooperates to disentangle the role played by our gut microbiota, via interactions with lifestyle factors (e.g. diet, eating habits, stress, etc.), in the regulation of pathways leading to the development of obesity and behavioural disorders. In this review the views of the Consortium in relation to diet and mood and how such effects are mediated by the microbiota are laid out.

New paradigm in mental health

The brain-gut-microbiota axis is the focus of the latest paradigm not just in neuroscience, but specifically in relation to mental health, and has been put forward as a potential watershed development (9). There is now an ever accumulating volume of evidence to support the fact that gut microbes have a major impact on central neurochemistry and behaviour, especially

stress related responses(10). In humans functional MRI (11) and electroencephalography(12) have been used to support animal studies. Through what mechanism(s) do gut microbes exert such significant central influence and how might targeting the brain-gut-microbiota axis through dietary intervention yield effective therapies for patients with depression?

In reviewing the published literature on the brain-gut-microbiota axis and mental health the main limitation at this point is the paucity of well designed, adequately powered clinical studies. As has been pointed out elsewhere, a majority of papers so far published are from the pre-clinical arena (9). Drawing major clinical conclusions from rodent studies is problematic.

Brain-gut microbe communication

It is argued that gut microbe to brain communication is a black box of which we have limited understanding (13). However, this may be considered as an overly pessimistic analysis of the current state of knowledge. We know that the brain-gut-microbiota axis is a bidirectional communication system which enables gut microbes to communicate with the brain, and the brain in turn to communicate with the gut (14). While brain-gut communication has been the subject of research for decades an exploration of gut microbes as an important vehicle within this context has only recently been proposed. The mechanisms of signal transmission are complex and involve neural, endocrine, immune, and metabolic pathways. Preclinical studies have implicated the vagus nerve, that long meandering nerve, as a fundamental neural route of communication between gut microbes in the periphery and centrally-mediated behavioural effects, as demonstrated by the elimination of central *Lactobacillus rhamnosus* (JB1) effects following a full truncal vagotomy (15). Epidemiological studies have demonstrated that individuals who underwent a full truncal vagotomy for treatment of peptic ulcer disease have a diminished risk of Parkinson's disease as they age (16). The gut microbiota also regulates

brain monoamines, such as serotonin, by altering levels of precursors; for example *Bifidobacterium longum 35624* has been shown to increase plasma tryptophan levels and thus impact central 5-HT (17). Tryptophan is the amino acid precursor of serotonin and the human brain has limited storage capacity, therefore requiring a continuous supply from the periphery. This supply originates from both a dietary source and from intestinal bifidobacteria who can synthesise the molecule.

Intriguingly, many gut bacteria can synthesise and release neurotransmitters. *Lactobacillus* and *Bifidobacterium* species produce gamma-aminobutyric acid (GABA): *Escheridia*, *Bacillus* and *Saccharomyces spp*. produce noradrenaline: *Candida*, *Streptococcus*, *Escheridia and Enterococcus spp.* can produce 5-HT: *Bacillus* can produce dopamine: and *Lactobacillus* can produce acetylcholine (18, 19). These gut-originated neurotransmitters can cross the mucosal layer of the intestine, though it is highly unlikely they directly influence brain chemistry. Even if they enter the blood stream, which has not been demonstrated, they cannot cross the blood brain barrier (BBB). Their impact on brain function therefore is most likely to occur by acting locally on the enteric nervous system. Short chain fatty acids (SCFAs), which include butyrate, propionate and acetate are metabolic products of gut microbial activity and are a rich energy source. They can exert central effects either through conventional GPCRs (G-protein coupled receptors), though such receptors are sparsely concentrated in the mammalian brain and the half-life of SCFAs is exceedingly short in the plasma. Alternatively, they may behave as epigenetic modulators by inhibiting histone deacetylases (HDACs)(20). The immune system provides another gut to brain communication pathway, signalling by way of cytokine molecules (21). Such molecules produced at the level of the gut can travel via the bloodstream to the brain. However, in normal physiological circumstances they do not cross the BBB, but there is accumulating evidence to support the view that they signal across the BBB and influence brain regions such

as the paraventricular nucleus of hypothalamus and circumventricular organs where the BBB is deficient. If plasma levels of the cytokines IL-1 and IL-6 are elevated by infection or otherwise they activate the core stress system, the HPA, bringing about the release of cortisol. This is viewed as the most potent activating mechanism of the stress system and is of special relevance in disorders such as the depression that emerges with interferon therapy for hepatitis or melanoma (22).

Psychopathology and gut dysbiosis

There is increasing evidence that some psychiatric disorders such as depression may be associated with a gut dysbiosis, a microbial imbalance. The extent to which such a dysbiosis is central to the pathophysiology of depression has yet to be been fully elucidated.

Depression

Lyte et al (23) found that oral gavage of the pathogen *Campylobacter jejuni*, in tiny subclinical doses, which failed to exert an immune response, resulted in anxiety-type behaviour in rodents. They also found that areas of brainstem, such as the nucleus tractus solitarius and lateral parabrachial nucleus, are involved in the processing that results in the autonomic, neuroendocrine and behavioural responses induced by the gavage.

A recently published epidemiological analysis supports the link between gut infection and anxiety. Bruch analysed the Medical Expenditure Panel Survey (MEPS) to prospectively determine a relationship between intestinal infection and future onset of an anxiety disorder (24). The data for all respondents who were 18 years of age or older and who did not have an anxiety disorder at baseline were included. Within the study population, there were 2577 subjects with an intestinal infection in Round 1 and 4239 with an anxiety disorder commencing subsequently. In total an intestinal infection in Round 1 was associated with a

significantly increased odds ratio of a subsequent emergent anxiety disorder. This major epidemiological study provides solid evidence for a link between intestinal infection and the development of anxiety.

O'Mahony and colleagues studied the gut microbiota in a maternal separation model of depression in rats (25). They reported an elevation in corticosterone in such animals, together with an increase in pro-inflammatory cytokines and a decrease in the diversity of gut microbes. In a recent study the fecal microbiota was sequenced in a depression study (26). Forty-six patients with depression and 30 healthy controls were recruited. High-throughput pyrosequencing showed that, according to the Shannon index, increased faecal bacterial alpha-diversity was present in those currently depressed but not in a group who had responded to treatment. This suggests that increased alpha diversity is a state rather than trait marker for depression. Bacteroidetes, Proteobacteria, and Actinobacteria were increased, whereas Firmicutes were significantly decreased. Despite the profound inter-individual variability, levels of several predominant genera differed between the depressives and controls. The depressives had increased levels of Enterobacteriaceae and Alistipes but reduced levels of Faecalibacterium. The authors conclude that further studies are necessary to elucidate the temporal and causal relationships between gut microbiota and depression and to evaluate the suitability of the microbiome as a biomarker. In a study conducted at APC Microbiome Ireland depressed patients had elevated cortisol output together with decreased faecal microbial richness and surprisingly when rats were given a humanised microbiota from depressed patients, as opposed to healthy controls, they developed a depressive phenotype from both a behavioural and immune perspective(27).

Depression co-morbidity

Depression is frequently co-morbid with a variety of medical illnesses including cardiovascular disease, metabolic syndrome and the gastrointestinal disorder irritable bowel syndrome (IBS), which presents with abdominal pain or discomfort and an alteration of bowel habit in the absence of gross pathology. In IBS an increase in pro-inflammatory cytokines in the plasma has been reported(28) together with altered gut barrier function (29). The latter is thought to lead to a 'leaky gut' and the passage of inflammatory molecules such as lipopolysaccharide (LPS) from gram negative bacteria into the blood stream(30) with subsequent activation of the immune system via toll-like receptors. The maternal separation model of IBS supports the view of an altered gut microbiota in the condition together with a pro-inflammatory phenotype.

It is possible that a poor quality diet may bring about the altered microbiota observed in depression. Narrowing of dietary diversity with reduced intake of essential nutrients can reduce availability of substrates for specific microbial growth and this could contribute to the intestinal dysbiosis of depression.

Diet and the microbiota

Over recent decades, dietary patterns in Europe and elsewhere have undergone major compositional changes, with increased intakes of red meat, high fat foods, and refined sugars. This 'Westernization' of diets together with sedentary lifestyles results in modifications to the gut microbiota, which may at least partially contribute to the increasing incidence of chronic inflammatory disorders, such as cardiovascular disease, obesity, inflammatory bowel disorder and depression (31). If we are to improve the nutritional value of food and positively impact mental health, we need to more fully understand the biological interactions between the food and microbiota. Many human studies have assessed dietary impact on the gut microbiota but they are limited by the difficulties in controlling potential confounding variables especially

lifestyle behaviours. Studies are limited by the fact that the microbiota is sequenced from faecal samples which provides no detail of the microbiota in various gut regions. With these limitations in mind we have learned some useful lessons in relation to dietary patterns and microbiota composition.

Mediterranean diet and depression

There is increasing evidence to support the view that poor quality diet is a risk factor for major depression. Epidemiological studies have long demonstrated that those on a Mediterranean diet suffer from less depression (32). Diets rich in fruit, vegetables, grains and fish seem protective against depression while a diet of highly proceeded food and those with a high sugar content predispose to depression(33). However, the data upon which these conclusions are based are largely observational. There is a paucity of properly controlled studies.

A recent study from Australia used a randomized controlled trial (RCT) design to investigate the efficacy of a dietary program for the treatment of major depression(34). A structured dietary support, focusing on improving diet quality using a modified Mediterranean diet was compared to a social support control condition. Sixty-seven patients were recruited fulfilling criteria for major depression and scoring 75 or less, out of a possible score of 104, on a Dietary Screening Tool, a score which indicated a poor baseline diet. If patients were on antidepressant medication or undergoing psychotherapy, they were required to be on the same treatment for at least 2 weeks prior to study entry. The dietary intervention group showed a significantly greater improvement in depression scores between baseline and 12 weeks than the social support control group. Overall, the results of this trial suggest that improving diet may be a useful strategy for treating depression or at least as an adjunctive to conventional therapies. Another study by Forsyth and colleagues reaches similar

conclusions(35). Furthermore, evidence is accumulating to support the view that the way in which diet impacts health in general is mediated by the gut microbiota(36, 37).

If we assume that a Mediterranean diet is effective in the prevention and perhaps the treatment of depression, what components of such a diet mediate these effects?

Polyunsaturated fatty acid and mood

The brain is a lipid-rich organ containing mostly complex polar phospholipids, sphingolipids, gangliosides and cholesterol (38). These are involved in both the morphology and physiology of neurones. The glycerophospholipids in the brain contain a high proportion of polyunsaturated fatty acids (PUFA) derived from the essential fatty acids, linoleic acid and alpha-linolenic acid. The main PUFAs in the brain are docosahexaenoic acid (DHA) derived from the omega 3 fatty acid, alpha-linolenic acid, and arachidonic acid and docosatetraenoic acid, both derived from the omega 6 fatty acid, linoleic acid(39).

Omega-3 fatty acid is derived from fish oil and there is considerable epidemiological evidence to indicate that those with a diet rich in fish have a lower incidence of cardiovascular disease than those with other diets(40). In recent times, the focus of attention has been on the impact of omega-3 fatty acids on depression. Studies indicate that in countries where there is a high consumption of fish there are lower rates of depression(41). However, in many European countries in recent decades the intake of omega-3 PUFAs has declined with a concomitant increase in omega-6 PUFA intake(42). Hibbeln was one of the first to draw demonstrate the importance of omega-3 PUFAs in mental health: in a cross-national study he found a significant negative correlation between worldwide fish consumption and prevalence of depression (43). Subsequent studies have found altered omega-6/omega-3 ratios in the plasma of depressed patients (44) and altered red blood cell

phospholipids (45). In post-mortem brain tissue lower DHA levels have been found in the orbitofrontal cortex of in depressed patients.

Nemets and colleagues studied 22 depressed patients who failed to respond to antidepressant therapy(46). The study had a parallel group, double-blind design in which EPA or placebo was added to the on-going antidepressant. A significant effect of omega-3 compared with placebo was found by week three of treatment. Peet et al examined the effects of EPA in 70 patients who had antidepressant resistant depression (47). Patients were randomised to receive either placebo or EPA in doses of 1, 2 or 4 grams per day for 12 weeks. They continued their antidepressant throughout. Forty-six of the 52 patients receiving the EPA and 14 of the 18 patients receiving placebo completed the 12 weeks study. The 1 gram per day group showed a significantly better outcome than the placebo group. The authors conclude that EPA 1 gram per day is an effective strategy for augmenting antidepressants in those who are treatment resistant.

The results with DHA are inconclusive. Thirty-six subjects with major depression assigned to receive DHA (2 g/d) for 6 weeks did not show differences in the score of the Montgomery-Asberg Depression Rating Scale compared with the placebo-treated group (48). A number of open label studies without appropriate controls report benefits. Given the lack of a placebo control, these results need to be viewed with caution (49) .

A recent meta-analysis of fifteen trials (916 total participants) using omega-3 PUFAs as either a mono or adjunctive therapy were analysed. Studies were selected based on prospective, randomized, double-blinded, placebo-controlled study design, if depressive episode was the primary complaint with or without comorbid medical conditions and, if appropriate outcome measures were used to assess depressed mood (50). This meta-analysis concluded that n-3 PUFA supplements with >60% of EPA (in a dose range of 200 to 2200

mg/d in excess of DHA) ameliorated the clinical condition. However, doses containing primarily DHA or <60% EPA were not effective against primary depression.

It is known that EPA has a general immuno-suppressive effect with a capacity to suppress inflammatory states. This may be relevant in the context of depression which is known to be associated with an increase in the acute phase protein C-reactive protein (CRP) and pro-inflammatory cytokines. A recent study demonstrated the capacity of polyunsaturated fatty acids to impact the brain-gut axis by increasing levels of bifidobacteria (51). At this point it seems reasonable to recommend fish in the diet of patients with depression but there is insufficient data to recommend omega-3 PUFAs as either a mono or adjunctive therapy in the disorder.

Probiotics and depression

Fermented foods have long been associated with a health benefit but only recently has that benefit been extended to mental health. Numerous claims of therapeutic efficacy have been made for probiotics but most claims are not substantiated by rigorous placebo controlled studies. Psychobiotics are defined as bacteria which when ingested in adequate amounts have a positive mental health benefit (52).

One therapeutic area where the benefits of probiotics have been established is in the common gastrointestinal disorder IBS. Several placebo controlled studies indicate that a bifidobacteria is highly effective in treating the condition(53). This is of relevance given the fact that up to 40% of patients with IBS have co-morbid depression and many bifidobacteria have anti-inflammatory activity.

The principal rationale for the use of probiotics in treating major depression rests on their potential for suppressing the pro-inflammatory component of depression. Can probiotics/psychobiotics alter this aberrant immunology? It was shown that a bifidobacteria in IBS switched the balance from a pro- to an anti-inflammatory cytokine response (54).

They found that in response to bifidobacteria treatment there was an increase in anti-inflammatory IL-10 and a reduction in pro-inflammatory IL-12 activity. Similar findings have been reported with *Lactobacillus acidophilus* (55).

There are several animal models of depression used for drug development. Using the maternal separation model, *Bifidobacterium longum* 35624 was found to normalise behaviour (17) and reduce corticosterone levels. This may indicate that the specific bifidobacteria strain has an antidepressant action.

In a recent study, Benton and colleagues used a placebo controlled design to examine the impact of probiotics on mood in healthy community based subjects. One-hundred and thirty-two subjects with a mean age of 62 years were recruited(56). Over a three week period they consumed either milk containing a probiotic or placebo daily. Mood was assessed at baseline and after 10 and 20 days of treatment. Those who rated their mood as poorest at baseline reported on average an improvement on probiotic by the end of the study. This improvement was not noted on placebo. Whether these findings translate to a clinical sample remains to be seen.

The effects of *Lactobacillus rhamnosus* HN001 given in pregnancy and postpartum on symptoms of maternal depression and anxiety in the postpartum period was assessed (57). Two hundred and twelve women were randomised to HN001 and 211 to placebo. Women who received HN001 had significantly lower depression and anxiety scores in the postpartum period. The results strongly support the view that the psychobiotic is protective against the emergence of postpartum symptoms. This is the best human intervention study so far in the literature.

Overall, it seems reasonable to conclude that psychobiotic studies in depressed patients are urgently required.

Prebiotics and depression

Prebiotics are fibres metabolised by the microbiota and capable of increasing the levels of good bacteria such as bifidobacteria. Prebiotics are found in vegetables such as celery, Jerusalem artichoke, garlic etc. A number of small clinical controlled trials have assessed the efficacy of certain prebiotics on psychological outcomes with promising results. Schmidt and colleagues demonstrated that 3-week supplementation with a galactooligosaccharide (GOS) prebiotic, which has been shown to stimulate bifidobacterial growth, in healthy volunteers significantly reduced waking cortisol response, the stress hormone strongly linked to anxiety and depression (58). Moreover, a B-GOS cohort demonstrated altered behavioural outcomes through a decrease in attentional vigilance to negative versus positive information in a dot-probe task compared to placebo. It is interesting to note, however, that fructooligosaccharide (FOS) supplementation had no effect. These results suggest that shaping of microbiota composition through prebiotic intake could influence behavioural outcomes. In humans, prebiotic supplementation with trans-GOS not only enhanced bifidobacterial growth and improved bloating symptoms, but in addition significantly reduced anxiety scores in IBS sufferers (59).

Polyphenols

Polyphenols are undoubtedly the most numerous among the groups of phytochemicals present in plants. They are broadly divided into flavonoids and non-flavonoids. Resveratrol which is found in red wine has potent CNS actions. In an animal model of depression it has been shown to reduce depressive type behaviours while attenuating the release of both corticosterone and pro-inflammatory cytokines (60). It also exerts anti-oxidant activity acting through sirtuins, is known to be metabolised by the microbiota and influences the Firmicutes/Bacteroidetes ratio in the intestine (61). To date there are no published controlled trials of resveratrol in depressed patients.

The polyphenol natural product curcumin possesses a variety of biological and pharmacological properties. Curcumin was found to reduce salivary cortisol levels in depressed patients relative to that seen in the placebo group(62). Recent data also indicates an impact in increasing gut microbial diversity (63).

MyNewGut Consortium recommendations

The Mediterranean diet is associated with lower rates of depression, impacts optimally on the gut microbiota and increasing evidence indicates that such a diet has antidepressant effects(64). Patients with depression or vulnerability to depression should be encouraged to enhance a plant-based diet with a high content of grains and fibres. High fibre diets are associated with fewer symptoms of depression. When analyzed by the source of fiber, diets higher in total fiber (more than 27 grams per day), and fiber from vegetables and breads/cereals (mostly whole grain) were associated with a 42%, 46%, and 41% reduced likelihood of having depressive symptoms, respectively(65). A decreased consumption of red, meat especially of processed meat(66), a regular intake of fish(67) and fermented foods(68) should be recommended. The intake of sodium and refined sugar should be restricted. Vigorous aerobic exercise consistent with the age and physical health of the patient should be encouraged(69).

Author contributions

TGD drafted the original manuscript. All authors contributed to discussion, editing and approval of the final manuscript.

Conflicts of interest

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Figure Legends

Fig. 1 Shows how stress and poor diet combine to produce a gut dysbiosis and the symptoms of depression

Fig. 2 Shows foods with high prebiotic content and capable of stimulating the growth of ‘good’ bacteria