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Nutritional considerations in major depressive disorder: current evidence and functional testing for clinical practice

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Abstract

Depression is a multifaceted condition with diverse underlying causes. Several contributing and inter-related factors such as genetic, nutritional, neurological, physiological, gut-brain-axis, metabolic and psychological stress factors play a role in the pathophysiology of depression. This review aims to highlight the role that nutritional factors play in the aetiology of depression. Secondly, we discuss the biomedical and functional pathology tests which measure these factors, and the current evidence supporting their use. Lastly, we make recommendations on how practitioners can incorporate the latest evidence-based research findings into clinical practice. This review highlights that diet and nutrition greatly affect the pathophysiology of depression. Nutrients influence gene expression, with folate and vitamin B12 playing vital roles in methylation reactions and homocysteine regulation. Nutrients are also involved in the tryptophan/kynurenine pathway and the expression of brain-derived neurotrophic factor (BDNF). Additionally, diet influences the hypothalamic-pituitary-adrenal (HPA) response and the composition and diversity of the gut microbiome, both of which have been implicated in depression. A comprehensive dietary assessment, combined with appropriate evaluation of biochemistry and blood pathology, may help uncover contributing factors to depressive symptoms. By employing such an approach, a more targeted and personalised treatment strategy can be devised, ultimately leading to improved patient outcomes.

Keywords: **functional pathology: major depressive disorder: nutritional medicine: nutritional psychiatry**

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Introduction

Depression is a multifactorial and polygenic disorder with considerable global importance. It is characterised by a range of physical, mental, and emotional symptoms which include depressed mood, diminished interest or pleasure, lack of energy, insomnia, agitation, a lack of concentration or indecision, feelings of worthlessness, and suicidal ideation[1]. Mental health disorders such as depression are known to substantially affect quality of life through impacting a person's ability to participate in meaningful roles and interact successfully with others[2]. There are numerous consequences associated with depression mental health, such as distress, disability, discrimination, lowered self-esteem, isolation, reduced social participation, and reduced personal and family income[3]. Quality of life is further diminished in individuals with depression[4] due to an increased risk of concurrent health issues, disease states, and co-morbidities including metabolic and endocrine disorders, as well as cardiovascular and inflammatory diseases[5].

The causes of depression are multifaceted and complex and include contributing and inter-related factors such as genetic, nutritional, neurological, physiological, gut-brain axis, metabolic and psychological stress factors[6,7]. Notably, recent and accumulating research in the field of nutritional psychiatry highlights a link between nutrients, foods and dietary patterns and risk of depression[7–10]. Numerous nutritional factors have been identified as playing causative or sustaining roles in depression. These include the tryptophan/kynurenine degradation pathway[11,12], one-carbon metabolism[13–15], homocysteine[13–15], the health and diversity of the microbiome[16–18], and certain nutrient deficiencies[13,19–21]. It is therefore crucial that these nutritional factors are investigated and addressed by qualified health professionals who can investigate potential underlying causes and drivers of depression in a holistic and comprehensive way.

Nutritional medicine practitioners subscribe to a holistic model of care which focusses on prevention, treating the whole person, finding and treating the root cause, and maximising the patients' agency to achieve mental and physical balance and restore their own health[22]. This is often achieved by using individualised non-reductionist approaches to treatment[23]. Given the multifaceted and complex nature of major depressive disorder, nutritional medicine practitioners are well situated to

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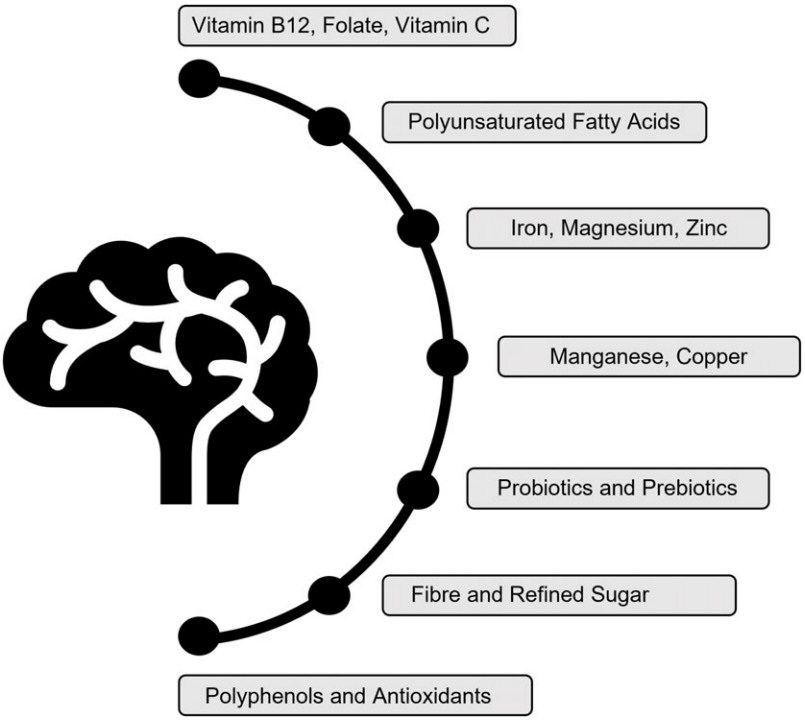

Fig. 1. Nutritional factors which impact depression.

investigate and address both the underlying biological drivers and contributing factors affecting impacting individuals with depression.

Therefore, there are several aims of this review. Firstly, to highlight the role that nutritional factors play in the aetiology of depression. Secondly, to discuss the biomedical and functional pathology tests which measure and assess these factors, and the current evidence supporting their use. Lastly, recommendations are made on how practitioners can incorporate these latest evidence-based research findings into clinical practice.

The causes of depression

The causes of major depressive disorder (MDD) are still uncertain and not fully understood; however, numerous studies point to several underlying and contributing factors, such as genetic[24], biological[25], psychological[26], social[27], lifestyle[28], environmental[29], and socio-economic factors[30]. Many of these factors can be evaluated via biomarkers, which are medical signs within the body that provide an objective measure of a patient's medical state[31]. Biomarkers influence or predict the occurrence or outcome of disease and include any substance, structure, process or their products that are measurable in the body[32]. Potential biomarkers implicated in the development and progression of depression and depressive symptoms include nutritional status, genetics and gene expression, hormone levels, and markers of inflammation and oxidative stress[31]. Dysregulation of any of these biomarkers may influence depression mental health outcomes and warrant investigation[31].

The role of social nutritional factors in depression

When exploring which nutritional factors may be influencing depressive symptoms, it is crucial that a holistic and person-centred approach is used. Therefore, assessing and acknowledging individual, social, and psychological factors which may influence food intake and mood, must also be carefully considered[33]. For example, gathering information on appetite, traditional or cultural food consumption, food security, intuitive eating practises and their relationship with food is crucial to deepen our understanding of the food–mood relationship for each individual person. Previous studies have highlighted the significant way that these social factors can influence food and mood[33,34]. These include: improving mood by removing food restriction[34], the effect of familial and cultural influences of food and mood[33], and how food nostalgia can impact mood[33]. Therefore, it is important that these factors are evaluated thoroughly, alongside the functional tests presented in this review. We will now outline several nutritional factors, their role in the aetiology of depression, and the biomarkers which can be tested (see Figs. 1 and 2).

The role of genetic factors in depression

There is a complex interaction between genetic and non-genetic factors regarding depression[35]. Research shows that susceptibility genes potentially interact with each other and with the environment, which is often referred to as a gene–environment interaction[36]. Mounting evidence suggests a relationship between genetic variants (polymorphisms) and depression[35], indicating that a predisposition towards the development of

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depression can be inherited[37]. A meta-analysis on all MDD case–control gene association studies found 393 polymorphisms in 102 genes associated with depression[35]. The review found six susceptibility genes which may be implicated in MDD. These genes include: *apolipoprotein E (APOE), guanine nucleotide-binding protein (GNB3) 825T, dopamine transporter (SLC6A3) 40 bp VNTR, dopamine receptor D4 (DRD4), methylenetetrahydrofolate reductase (MTHFR) 677T*, and *serotonin transporter (SLC6A4) 44 bp ins/del*[35].

Specific genes have been researched in regard to their exposure to environmental factors and how these factors influence subsequent outcomes[38]. For example, the *serotonin transporter (5-HTT) gene*, and its two promotor variants have been studied in regard to its interaction with stressful life events and predisposing potential towards depression[39]. It is speculated that the interaction of only a few, rather than many genes and their variants, such as the *5-HTT gene*, are conditionally affected impacted by an individual's exposure to environmental risks, and may be an underlying cause of depression and other multifactorial disorders[39].

The role of methyltetrahydrofolate reductase (MTHFR) gene in depression

Several key nutrients, such as folate and vitamin B12 (cobalamin) are involved in gene expression and genomic stability[40]. Folate is crucial for optimal brain and cognitive function, mental health and mood regulation[41]. Furthermore, folate is essential for DNA and RNA synthesis. Methyltetrahydrofolate reductase (MTHFR) is an enzyme responsible for the irreversible reduction of 5,10-methyltetrahydrafolate to the primary active form of folate, 5-methyltetrahydrafolate (5-MTHF)[42]. In metabolic reactions, folate acts as a donor or acceptor of one-carbon units required for one-carbon metabolism, and the methionine cycle[40]. The intermediate products of this metabolic cycle include a methyl donor (for example methionine, folate, betaine and choline) and S-adenosyl-L-methionine (SAMe)[40].

The production of a methyl donor is necessary for the synthesis of the amino acid methionine from homocysteine[43]. This process is dependent on vitamin B12 (as a co-factor) and the presence of either of the active forms of vitamin B2 (reduced flavin adenine dinucleotide) or vitamin B3 (reduced nicotinamide adenine dinucleotide)[43]. Furthermore, methionine is the precursor of SAMe, the universal methyl donor used in cellular methylation, whereby SAMe donates a methyl group (CH_3) to another molecule, causing it to become bioactive[43]. Upon donating its methyl group, SAMe transforms into S−Adenosyl homocysteine which is rapidly converted to homocysteine and completes the methylation cycle[43]. Therefore, MTHFR indirectly regulates the recycling of homocysteine and thus circulating homocysteine levels, which is known to be associated with depression and depressive symptoms[44].

The gene that encodes the MTHFR enzyme is called the *MTHFR gene*. There are several genetic variants (polymorphisms) of this gene that have been identified and researched in relation to their influence on *MTHFR* activity[45]. Polymorphisms of this gene have been found to be associated with depression. Such polymorphisms are *MTHFR C677T* and *A1298C*[45]. The *MTHFR C677T* genotype results in MTHFR taking on a thermolabile state where, due to exposure to heat, the enzyme is inactivated or loses its characteristic properties in addition to reduced activity[43]. Furthermore, the genotype *MTHFR C677T TT* is associated with a 25% mean increase of homocysteine levels compared with *MTHFR C677T CC* homozygotes, although this is dependent on folate status[43]. An accumulation of homocysteine can result in an abnormally high level of homocysteine in the blood (hyperhomocysteinaemia). Hyperhomocysteinaemia affects vascular endothelial cells and neuronal cells, dysregulating neurotransmitter synthesis and consequently resulting in psychological disturbances and illnesses, including depression[46].

The involvement of vitamin B12 and folate in single-carbon transfer reactions enables the production of serotonin and other monoamine neurotransmitters involved in the regulation of mood[47]. Therefore, hyperhomocysteinaemia and folate deficiency are prospective risk factors for depression. Conversely, lowered homocysteine levels are associated with lowered depression symptoms[48]. As the genotype *MTHFR C677T TT* is associated with hyperhomocysteinaemia, it is hypothesised that folate supplementation in this group will confer a protective effect on depression[49]. Testing for homocysteine, MTHFR polymorphisms, folate and B12 can be achieved via blood pathology, and are generally available through a general practitioner referral or functional medicine pathology labs.

The role of metabolic factors in depression

Disturbances within metabolic pathways, including the dysregulation of glucose, insulin, leptin, tryptophan and serotonin, are commonly observed in patients with depression[50–52]. Furthermore, studies suggest metabolic disturbances along these pathways may provide a link between depression and metabolic syndrome, obesity and CVD[50] due to the sharing of these common metabolic pathways[50,53].

It has been proposed that hyperglycaemia may modify hypothalamic–pituitary–adrenal (HPA) axis function, which leads to an increased risk of depressive symptoms[54]. Additionally, hyperglycaemia and insulin resistance may lead to depression due to increased oxidative stress[55]. Hyperglycaemia can lead to a reduction of antioxidant enzymes in the brain, resulting in an accumulation of reactive oxygen species (ROS)[55]. ROS cause cell damage and cellular death, resulting in cerebral injury and inhibition of neurogenesis. Furthermore, ROS activate NF-κB, thereby up-regulating the expression of pro-inflammatory cytokines such as TNF-α, interferon gamma, cyclooxygenase-2 and IL-1β[56]. This increase in neuroinflammation is thought to be a key contributor in the pathogenesis of depression due to the resulting activation of the HPA axis, the reduction of brain-derived neurotrophic factor (BDNF) and the induction of indoleamine 2, 3-dioxygenase (IDO)[55]. IDO plays a crucial role in the tryptophan–kynurenine pathway and prolonged activation is thought to contribute to reduced serotonin production[57]. Therefore, testing patients fasting blood glucose and HbA1c should be considered in patients with depression where hyperglycaemia is suspected to

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be a contributing factor. Assessing dietary intake of refined, added and excess sugar is also warranted.

Leptin is an adipokine that exerts neuroendocrine regulatory functions on energy balance and glucose metabolism[58]. Diet-induced obesity can lead to leptin resistance, and further exacerbate overeating. Leptin also influences several psychological functions including cognition, motivation, and memory, in addition to its effects on neuronal structure, survival and plasticity[59]. Leptin receptors are extensively dispersed throughout the brain, impacting several neurotransmitter systems. Leptin has both metabolic and neurological properties involved in neuroprotection, cognition and mood, and therefore has been associated with depression[5]. It modulates the mesolimbic dopamine pathway, HPA axis function, hippocampal synaptic plasticity and serotonin synthesis[58]. Leptin influences serotonin via inhibition of nitric oxide synthase, which facilitates the normal action of serotonin on its receptors and its reuptake by serotonin transporters[60]. Consequently, leptin resistance and the associated decreased nitric oxide synthase leads to the inhibition and transformation of serotonin into inactive dimers[60]. Therefore, underlying leptin resistance may play a role in depressive symptoms[61]. While serum blood tests can ascertain leptin levels, healthcare providers do not routinely test leptin levels and the test is not available at all laboratories. As dietary factors, including increased fat and sucrose intake and low protein consumption, are drivers of leptin resistance, a thorough dietary analysis should be undertaken.

As mentioned previously, alterations to the tryptophan–kynurenine (KYN) pathway[62] can result in depleted levels of serotonin[62]. Under normal circumstances, less than 3% of tryptophan metabolism is directed down the serotonin branch, while approximately 95% is directed down the kynurenine pathway[63]. The activation of the kynurenine pathway and the consequent generation of neurologically active metabolites are implicated in several psychiatric disorders including depression, schizophrenia, and bipolar disorder[63]. The enzymes indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO) are the first and rate-limited step of catalysing the conversion of L-tryptophan into N-formylkynurenine[63]. N-Formylkynurenine is then further degraded to either picolinic acid (neuroprotective) or quinolinic acid (neurotoxic)[64]. Quinolinic acid is considered neurotoxic due to its activation of N-methyl-D-aspartate receptors and free radical production[64]. It may also promote interferon gamma-induced inflammation and has been strongly associated with depression and neurodegenerative diseases[64].

Neuroinflammation can lead to excessive production of quinolinic acid and further alterations to the picolinic acid/quinolinic acid ratio[64]. Specific nutritional factors have been shown to influence quinolinic acid levels and reduce quinolinic induced damage. These include probiotics[65], polyphenols[66] and essential fatty acids[67]. Assessing intake of these dietary components may therefore be valuable. Currently, there are no widely available tests for IDO and TDO. Some functional pathology labs assess tryptophan and associated metabolites via urine organic acid tests; however, many of these tests have not been adequately assessed for validity and reliability, so caution should be used when interpreting results. Further, urine levels of quinolinic acid are not a reflection of its levels in the brain[68]. The same applies for organic acid test of 5-hydroxyindoleacetic acid (5-HIAA), a metabolite of serotonin. Levels measured in urine are often used as a marker to determine the levels of serotonin in the body. However, urinary levels of 5-HIAA, do not reflect levels found in the brain or cerebrospinal fluid[69].

The role of inflammation and Immunological factors in depression

Interactions between the central nervous system and immune system have been studied to assess immune activation in depression. It has been suggested that, from an evolutionary perspective, the inflammation response and symptoms of depression formed an integrated adaptive response to pathogens that enabled wound healing and allowed individuals to avoid subsequent pathogen exposure[70]. Crosstalk between the various inflammatory pathways and neurocircuits within the brain can result in altered behaviour, such as avoidance and anxiety[70]. This may have provided an evolutionary advantage to early humans in regard to their interactions with predators and pathogens. However, in today's modern world, sustained high levels of inflammatory cytokines may be driving increased levels of depression[70].

Cytokines, such as IL-1β, IL-4, IL-6, IL-10, TNF-α and C-reactive protein (CRP)[5,71], are signalling molecules involved in immune regulation, specifically regulating a host's response to immune processes, inflammation, infection, and trauma. Cytokines can have either pro- or anti-inflammatory actions within the body. An increase in the levels of inflammatory cytokines and the induction of their signalling pathways, in addition to the activation of various immune cell subsets have been observed in the peripheral blood and brain of depression patients[70]. CRP, TNF-α, IL-1β and IL-6 are the most consistently raised inflammatory markers in patients with depression[70]. Assessing CRP may therefore be a useful tool in determining the extent that inflammation may be contributing to patient symptoms and may assist with monitoring the effectiveness of treatment strategies[72]. Extensive research demonstrates that diet can affect circulating markers of inflammation. Findings from a recent meta-analysis indicated that CRP concentration is positively associated with sugar intake, and negatively associated with the consumption of vitamins, minerals and polyunsaturated fatty-acids, suggesting inflammation is likely influenced by dietary intake[73].

Accumulating evidence has also demonstrated that the Kelch-like ECH-associated protein 1 nuclear factor (erythroid 2-derived)-like 2 (Keap1-Nrf2) system may be involved in depression pathogenesis, via its key role in regulating inflammation and oxidative stress[74]. The Keap1-Nrf2 system can influence the body's response to oxidative stress by regulating the activity of Nrf2, a transcription factor that promotes the expression of antioxidant genes and other protective mechanisms[74]. When this system is disrupted or impaired, it can lead to increased oxidative stress and inflammation, which may contribute to the neurobiological changes associated with depression[74]. Some studies have shown that dysfunction in the Keap1-Nrf2 pathway may be associated with depressive

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symptoms and that dietary interventions, such as sulforaphane, aimed at enhancing Nrf2 activity could potentially have antidepressant effects[75,76]. However, there are currently no widely used clinical tests specifically designed to measure the activity of the Keap1-Nrf2 system in a routine medical setting.

The role of hormones in depression

Impairments in hormones and endocrine function may play an important role in the underlying pathophysiology of depression[77]. Abnormalities in adrenal (HPA axis) and thyroid (HPT axis) function are often associated with altered mood, and medications which target endocrine function, often lead to mood-related and cognitive effects[77].

Research has demonstrated that in patients with depression, glucocorticoid receptor (GR) signalling is abnormal and associated with chronic hypersecretion from the corticotrophin releasing hormone neurons of the HPA axis[78]. It is thought that this chronic hypersecretion may shift HPA activity toward increasingly higher set points, which may result in persistently elevated HPA activity often observed in patients with depression[78]. Unhealthy dietary habits, and the consumption of unhealthy foods, for example, foods high in carbohydrates or fat, have also been connected to HPA axis hyperactivity, and represent a significant contribution to stress accumulation[79]. Hypercortisolaemia can cause excitotoxicity leading to loss and atrophy of dendrites, as well as inhibition of neurogenesis in the dentate gyrus of the hippocampus[26]. Numerous studies conducted in patients with depression have shown abnormalities in the suppression of cortisol after pharmacological and psychological challenges[26]. However, the relationship between depression and cortisol is highly complex, and appears dependent on a range of different factors[78]. These factors include the stage and severity of illness, and the type of challenge faced[78]. For example, research demonstrates that depressive symptom severity is proportionate to cortisol levels. However, the HPA response appears to be unaffected in chronic depressive states, such as in those experiencing symptoms for longer than two years, therefore measuring cortisol levels will not provide prognostic information in chronic major depressive disorder[78].

Thyroid hormones are responsible for a number of important functions within the body. Their primary function is the regulation of cell differentiation, metabolism and nervous system development[80]. Altered levels of thyroid hormones can lead to nervous system-related problems linked to cognition, vision, motor skills, language and memory[80]. Thyroid hormones have also been associated with neuropsychiatric disorders including bipolar disorder, schizophrenia, depression and anxiety[80]. Clinical hypothyroidism is commonly associated with depressive symptoms, and subclinical hypothyroidism is commonly reported in treatment-resistant depression[77]. However, most patients experiencing depression do not have clear biochemical evidence of thyroid disease[81]. Although, research does show that patients with depression often display low T3 levels, raised T4 levels, raised reverse T3 levels, a blunted thyroid-stimulating hormone response to thyrotropin-releasing hormone and positive antithyroid antibodies[81]. Further research exploring the various mechanisms involved in the interaction between thyroid function and depression needs to be conducted before firm conclusions can be drawn[81]. However, routine screening of patients presenting with depression for potential thyroid dysfunction should still be considered.

Several key nutrients are involved in healthy thyroid function. For example, thyroid peroxidase is a haem-dependent enzyme required for thyroid hormone synthesis, which only becomes active at the apical surface of thyrocytes after it binds a prosthetic haem group, therefore, adequate iron is essential for the synthesis of thyroid hormones[82]. Additionally, selenoproteins are required for healthy thyroid function. In the thyroid, several ROS, such as hydrogen peroxide (H_2O_2) are generated during iodine organification, which is the incorporation of iodine into thyroglobulin for the production of thyroid hormones[83]. The thyroid is protected from the harmful effects of ROS primarily by the antioxidant enzymatic system, comprising the antioxidant elements selenium, copper, manganese and zinc[83]. Assessing these trace elements via a food diary and blood pathology may therefore also be of value.

The role of neurological factors in depression

BDNF is a peptide involved in the maintenance and survival of neurons, synaptic integrity and synaptic plasticity[84]. The production and secretion of BDNF is compromised by inflammatory processes and endothelial dysfunction, resulting in low BDNF levels[85]. Research demonstrates that low levels of BDNF have been reported in patients with depression[79] and those with suicidal ideation[86]. Emerging evidence also suggests that the therapeutic action of many anti-depressive medications is due to their ability to reverse this decrease[84]. Numerous factors have been associated with low BDNF levels. For example, stress has been shown to modulate BDNF expression[87], and low BDNF levels have also been linked to food cravings, overeating and weight gain[5,88]. Several nutritional factors have been explored for their potential to increase BDNF levels[89]. These include polyphenols, omega-3 fatty acids, zinc and probiotics[89]. Assessing dietary intake of these nutrients may therefore be of value.

Depression has been associated with neurotransmitter imbalances, specifically serotonin, dopamine, noradrenaline and glutamate[90]. Deficiencies in serotonin availability, serotonin receptor abnormalities[91] and an increase in monoamine oxidase which metabolises serotonin in the brain[92], all support the neurotransmitter imbalance hypothesis for MDD[29]. The theory that depression is caused by low serotonin was first suggested in the 1960s and has been heavily promoted since the discovery of selective serotonin reuptake inhibitor antidepressants[93]. However, this theory of depression has received growing scrutiny in recent years. For example, this hypothesis does not explain why drugs such as tianeptine, which reduce rather than increase serotonin availability at the synaptic cleft, are effective antidepressants[94]. Further, a large meta-analysis of monoamine depletion studies concluded that monoamine depletion appears to only decrease mood in subjects with a family history of depression and in drug-free

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patients whose depression is in remission[95]. However, monoamine depletion does not appear to decrease mood in healthy individuals and fails to demonstrate a causal relationship[95]. Additionally, a large umbrella review published in 2022 found that research investigating the role of serotonin in depression concluded that there is no convincing evidence to support that depression is associated with, or caused by, reduced serotonin levels or activity[93].

Although several antidepressants alter monoamine levels within a few hours, changes in mood are typically not observed for approximately 3–4 weeks[96]. This discrepancy, coupled with the fact that antidepressants appear to increase the quantity of adult-born neurons, which take approximately 4 weeks to form synaptic connections, has created the hypothesis that antidepressants may affect mood via increasing the levels of adult hippocampal neurogenesis[96]. This plasticity hypothesis links depression with reduced hippocampal neurogenesis and neurotrophin levels[97]. The delayed therapeutic onset of antidepressant medications may therefore be explained by this hypothesis, in which the time lag is attributed to antidepressants changing various intracellular enzymes, for example, cyclic adenosine monophosphate, protein kinase A and adenylyl cyclase[97]. These enzymes activate the expression of the neuroprotective BDNF[97].

The role of the gut–brain axis in depression

An emerging field of study is demonstrating a strong link between the gut microbiota and the brain. Referred to as the gut–brain axis, an understanding of the role of the gut microbiota and its influence on alterations of the immune, neural and endocrine systems continues to develop[98]. However, influences are not unidirectional. The central nervous system through the activation of the HPA axis, autonomic nervous system and neuroendocrine systems, alters the composition, motility and secretion, and therefore gut microbiota equilibrium, thus directly impacting the gut microbiota[99].

The health of the gut and its microbiota have been linked with numerous neuropsychiatric disorders[100]. Gut bacteria are involved in the production of active metabolites via enzymatic reactions which result in products having therapeutic activity within the body[101]. For example, the monoamines serotonin, dopamine and norepinephrine can be derived from certain microbes. *Escherichia coli*, *Candida* and *Streptococcus* produce serotonin, *Bacillus* and *Serratia* produce dopamine, and *E. coli*, *Bacillus* and *Saccharomyces* produce norepinephrine[102]. Additionally, gamma-aminobutyric acid is synthesised by *Lactobacillus* and *Bifidobacterium*[102].

The body's immune system is supported by the role of the gut microbiota and its diversity[102]. Regulation of pro-inflammatory cytokines and chemokines, such as the interleukins IL-1, IL-8, IL-10 and transforming growth factor B occurs due to the interaction of gut bacteria with the gut mucosa. The gut mucosa covers the largest surface of epithelium in the body, and along with tight junctions in the gut epithelium, they form a physical barrier against bacteria, harmful substances produced by bacteria and antigens[102].

Alterations to the composition of resident gut microbiota, or dysbiosis, leave the gut epithelium wall susceptible to microdamage and increase its permeability, thereby allowing harmful substances to enter systemic circulation[102] and instigating an immune response. As the brain and stomach are directly linked via the vagus nerve, bacterial, hormonal and neuronal changes in the gut are transmitted directly to the brain. The vagus nerve, also referred to as cranial nerve number ten, is a principal component of the parasympathetic nervous system[103]. It is comprised of roughly 80% afferent and 20% efferent fibers. It plays a crucial role in interoceptive awareness, whereby it senses microbial metabolites through its afferents, and transfers this information to the central nervous system[103]. This information is then integrated into the central autonomic network, where a response is then generated.[103]. The gut microbiota and its metabolites can therefore affect the brain's development and plasticity by secreting neurotrophins and proteins, such as post-synaptic density (PSD)-95, BDNF and synaptophysin[102].

Additionally, stress is known to inhibit the vagus nerve and has harmful effects on the gastrointestinal tract and the microbiota[104]. Brief exposure to stress can have a notable impact on the composition of the microbiota community, causing shifts in the proportions of major microbiota phyla[104]. Moreover, when the gut microbiota is deliberately manipulated in experiments, it can affect an individual's responsiveness to stress and the threshold at which the neuroendocrine HPA axis becomes activated[105]. These alterations are associated with changes in microbiota-related metabolites and immune signalling pathways, suggesting that these systems could play a significant role in stress-related conditions, including depression[105].

Microbiome mapping has gained increasing popularity in recent years, with several companies offering a range of tests aimed at assessing the quality and diversity of the gastrointestinal tract microbiome. Some biotechnology companies market personalised microbiome testing directly to the public[106]. These tests range greatly in complexity and costs and aim to provide personalised diagnosis and therapies. Many companies provide detailed reports on the gut microbiota diversity, beneficial and pathogenic microorganisms which effect health and disease, and personalised dietary, supplemental and lifestyle advice[107]. However, current research evidence is not adequate to allow for meaningful diagnoses to be concluded, due to the high degree of inter-individual variability in the microbiome and the substantial limitations of the analytic methods most commonly used[106]. Over-extrapolation of results by the service provider and over-interpretation of results by patients poses a significant risk which may cause unnecessary stress and anxiety, dietary changes and supplement use, which may ultimately do more harm than good[107].

Although microbiome data are not diagnostic at present, data from commercial tests do provide patients with a snapshot of their microbiome in comparison to other individuals from different environments and backgrounds[106]. For example, abundances of particular genera which may contain true pathogens, may be informative regarding risk for specific illnesses[106]. More research is needed to explore changes to

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the microbiome in major depressive disorder to draw any firm conclusion about a patient's risk or diagnosis based on their microbiome profile.

The role of minerals in depression

Magnesium is an essential mineral required for the appropriate activity of many biochemical and physiological processes, including DNA replication, transcription and translation[108]. Previous research has demonstrated that magnesium is involved in various brain regions in the limbic system, consequently implicating magnesium in the aetiology and progression of depression[108]. However, current research is conflicting, with some studies demonstrating an increased risk of depression in those with low magnesium intake[109,110], and others finding no association[111,112]. The biological mechanisms involved between depression and low serum magnesium levels is currently uncertain; however, it is thought to include the central nervous system, HPA axis and oxidative stress pathways[113]. Research has shown that magnesium deficiency leads to changes in glutamatergic transmission in the limbic system and cerebral cortex. Additionally, magnesium's role as an antagonist of the N-methyl-D-aspartate glutamate receptor, a significant component involved in synaptic potentiation, learning and memory, is well established[113]. Research indicates that magnesium intake from the diet is insufficient in approximately 60% of adults, and that subclinical magnesium deficiency is widely prevalent in western populations[114]. Unfortunately, the evaluation of magnesium status is complicated due to a number of factors, with serum magnesium concentrations demonstrating no reliable correlation with total body magnesium levels or concentrations in specific tissues[114].

Iron is an important mineral which acts as a co-factor in the production of several neurotransmitters, including dopamine and serotonin. There has been a growing interest in the role of iron in neurodevelopment and its implication in psychiatric and neurological conditions[115]. Several studies have highlighted that iron deficiency is associated with an increased depression risk[19,116,117], and recent randomised clinical trials have demonstrated that supplementing with iron leads to reduced depressive symptoms[115]. It is therefore recommended that patients iron levels, particularly ferritin, are assessed to determine if iron deficiency could be a causative or contributing factor in depressive symptomology[115].

Another essential trace element required for numerous vital biochemical and physiological processes needed for brain growth and function, is zinc[118]. The ratio of intracellular and extracellular zinc levels is critical for zinc homeostasis in the brain, especially in regions linked with the pathophysiology of depression, for example the amygdala, cerebral cortex and the hippocampus[113]. A meta-analysis concluded that blood zinc concentrations were roughly 0·12 μg/ml lower in depressed patients compared to healthy controls[119]. Additionally, randomised controlled trials conducted in individuals with depression have observed improvements in symptoms of depression when participants combined antidepressant drug therapy with zinc supplements, compared with antidepressants alone[120,121]. It has been suggested that low zinc is associated with depression due to decreased neurogenesis and neural plasticity, increased cortisol levels, and a disturbance in glutamate homeostasis. Zinc's antidepressant action is thought to be due to increased expression of BDNF[113]. Zinc status is often measured via a blood test, urine test or hair analysis, which have all demonstrated to be reliable biomarkers of zinc status[122].

The role of polyunsaturated fatty acids in depression

Polyunsaturated fatty acids (PUFA), particularly omega 3 and omega 6, are found in high concentrations in the brain[123]. Clinical studies have demonstrated that patients diagnosed with depression or anxiety display significantly lower levels of PUFA in the blood and in the brain[124,125]. Furthermore, the cytochrome P soluble epoxide hydrolase pathway has been suggested to play a key role in depression[126]. Soluble epoxide hydrolase are enzymes which metabolise cytochrome P derived epoxy fatty acids to their corresponding diols. Evidence suggests that soluble epoxide hydrolase plays a key role in the anti-inflammatory effects involved in the metabolism of omega-3 PUFA[126]. Evidence also demonstrates that in patients with major depressive disorder, the protein expression of soluble epoxide hydrolase in the brain is higher than in healthy controls[126].

PUFA intake, particularly the omega-3 eicosapentaenoic acid (EPA) has been linked with depression via a number of different mechanisms. For example, increased intake leads to decreased production of proinflammatory cytokines, such as TNF-α, IL-1β, IL-2 and IL-6[123], and has been linked with increases in *N*-acetyl-aspartate in the brain, a key marker for neuronal homeostasis, which suggests a role as a neuroprotective agent[127]. EPA supplements have also been shown to increase the ratio of cerebral phosphomonoesters to phosphodiesters, a crucial marker of phospholipid turnover, in addition to reversing brain atrophy in patients with MDD[128]. EPA supplementation has also demonstrated an ability to increase BDNF levels after traumatic brain injury[123]. Lastly, EPA can increase dopaminergic and serotonergic neurotransmission[129]. PUFA can be measured via an Omega-3 Index test, which measures erythrocyte EPA and DHA content. This test is offered by a number of functional medicine pathology labs and has shown to be a reliable and valid measure of PUFA status[130,131].

Recommendations and key implementation strategies

Given the significant role that nutritional factors play in the pathophysiology of major depressive disorder, it is important that these factors are thoroughly and comprehensively investigated. For example, identifying if an undiagnosed iron deficiency or thyroid condition is a contributing factor to depressive symptomology may prevent unnecessary antidepressant medication prescriptions. Therefore, based on the latest evidence discussed in this review article, we recommend the following nutrients and associated biochemistry be assessed in patients displaying symptoms of depression (see Fig. 2).

Genetic factors: testing for homocysteine, folate and vitamin B12 can be evaluated via blood pathology and are routine tests

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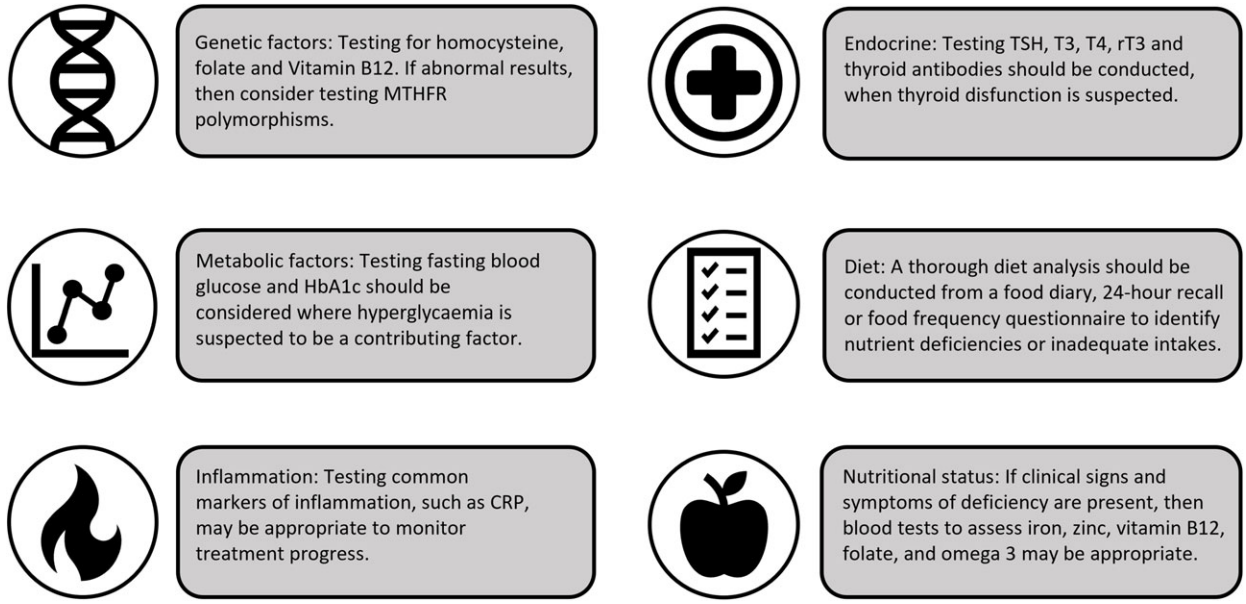

Fig. 2. Functional testing for depression.

available with a general practitioner referral. If patients present with elevated homocysteine and abnormal folate results, then testing MTHFR polymorphisms may also be warranted.

Metabolic factors: testing patients' fasting blood glucose and HbA1c levels should be considered in patients with depression where hyperglycaemia is suspected to be a contributing factor. Assessing the diet for refined, added and excess sugar intake is also warranted. Testing urine levels of quinolinic acid and 5-hydroxyindoleacetic acid (5-HIAA) is not recommended at this time.

Inflammation: much evidence shows that CRP, TNF-α, IL-1β and IL-6 are the most consistently raised inflammatory markers in patients with depression. Therefore, testing these markers may be a useful tool in determining the extent that inflammation may be contributing to patient symptoms and may assist with monitoring the effectiveness of treatment strategies.

Hormones: the association between depression and cortisol is highly complex and appears dependent on a range of different factors. HPA response does not appear to be affected in chronic depressive states, such as in those experiencing symptoms for longer than two years, therefore cortisol levels will not provide accurate prognostic data in chronic MDD. In patients presenting with signs and symptoms of thyroid dysfunction, a full thyroid panel including TSH, T3, T4, rT3 and thyroid antibodies should be conducted.

Gut–brain axis: at this stage, microbiome testing is not advanced enough to accurately determine if the microbiome composition indicates MDD. Testing may be warranted to rule out gastrointestinal pathogens, but should not be relied upon to direct treatment strategies for depression at this time.

Nutritional medicine and diet: in the first instance, we recommend that a thorough dietary analysis should be conducted from a food diary, 24-h food recall or food frequency questionnaire to identify potential nutrient deficiencies (e.g. iron, magnesium, zinc, vitamin B12, folate, PUFAs) or inadequate intakes. Nutrition analysis software programmes such as FoodZone[132] or FoodWorks[133] may assist in accurately capturing this information. If additional clinical signs and symptoms of deficiency are also present, then further testing may also be necessary. Blood tests to assess iron, zinc, vitamin B12, folate and omega 3 are recommended; however, blood tests for magnesium are not recommended at this time.

Conclusion

As heterogeneous as depression's causes are, it begs the question, why is its treatment predominantly homogeneous? There are numerous factors which are associated with the causes of depression, which consist of non-modifiable and modifiable factors. These factors should be thoroughly investigated by nutritional medicine practitioners and qualified professionals to inform individual treatment approaches. Diet and nutrition play a fundamental role in the aetiology of depression. Diet affects the expression of genes with folate and vitamin B12 being vitally important for methylation reactions and homocysteine regulation. Nutrients are involved in the tryptophan/kynurenine pathway and are involved in the expression of BDNF. Diet also influences the HPA response and the diversity and composition of the gut microbiome. Comprehensively assessing dietary intake, and where appropriate, assessing patients' biochemistry and blood nutritional markers, may help uncover important contributing factors to patients' depressive symptoms. This will lead to a more targeted and personalised treatment strategy, which may ultimately improve patient outcomes.

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Competing interests

The authors have no conflicts of interest to declare.

Authorship

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