Clinical nutrition for depression

Overview
Clinical depression is a disorder of both immune and inflammatory function and is accompanied by ongoing activation of the hypothalamic pituitary adrenal (HPA)-axis, likely as a result of chronic stress.[1, 2] The immune system responds to stress by releasing pro-inflammatory cytokines, derived from arachidonic acid (AA, omega-6); these trigger a number of metabolic pathways including those that alter serotonin production and uptake. Omega-3 fatty acid deficiency, which is common in clinical depression, influences the delicate balance of omega-6 and omega-3 fatty acids, resulting in accumulation of membrane AA. This has a corresponding effect on pro-inflammatory mediators and central serotonin production, all of which appear to be normalised by eicosapentaenoic acid (EPA, omega-3) supplementation. The evidence for EPA in treating depression, in normalising dysregulated inflammation, highlights EPA as a promising and successful alternative to standard pharmaceutical interventions for this crippling condition.

Omega-3 levels in the depressed patient
Deficiencies and imbalances of omega-3, not only during foetal development but also throughout the whole life span, have significant effects on brain function.[3] The principal genes FADS2 and FADS1 that code for the delta-6 and -5 desaturase enzymes involved in PUFA biosynthesis, are known to be down-regulated in major depressive disorder patients, [4] as reflected by the significantly low levels of omega-3 levels observed in patients.[5-7] The omega-3 index (EPA + DHA) is a validated biomarker of cardiovascular health [8], and there is increasing call for its use as a biomarker for mood disorders. [9] Alterations in fatty acids in clinical depression include a decrease in omega-3 fatty acids and an increased omega-6 to omega-3 ratio, specifically AA to EPA, correlating positively with symptom severity. [7, 10] Deficiencies in omega-3 and increased omega-6 AA concentrations can result in increased levels of prostaglandin E2 (PGE2), known to directly activate the HPA-axis, increase cortisol and drive the production of inflammatory mediators. The HPA-axis is the infrastructure of the body, which regulates the stress response. Controlled by an intricate network of neuronal and hormonal pathways, abnormal HPA-axis activity is routinely observed in patients with major depressive disorder.[11]

Inflammation and depression
Cytokines are the principal chemical mediators of the inflammatory response and can be categorised as either pro-inflammatory or anti-inflammatory. Over-production of pro-inflammatory cytokines (such as IL-1β, IL-6, IL-12, IFN-γ and TNF-α), as a result of prolonged or intensive stress, results in various dysfunctions of the body, including anxiety, impaired attention and memory, and sleep disturbance – all of which are key players in the onset and progression of mood disorders[12].
Both cortisol and inflammatory cytokine production increase the risk of developing depression by altering the activity of enzymes from key metabolic pathways including indoleamine 2,3-dioxygenase (IDO) tryptophan 2,3-dioxygenase (TDO) and kynurenine monoxygenase (KMO). The alternative metabolism of tryptophan by IDO- and TDO- results in kynurenine production and a subsequent reduced production of the neurotransmitter serotonin. The chronic up-regulation of the kynurenine pathway due to activation of TDO, up-regulated by cortisol, and IDO activated by cytokines [13] results in an imbalance in critical neuroactive compounds, including a reduction of tryptophan, a reduction of serotonin and elevation of tryptophan-derived metabolites. In addition, increased cytokine levels activate KMO, which results in the production of the neuroprotective product kynurenic acid from kynurenine and increases the production of quinolinic acid, which has potent neurotoxic effects.[14] Pro-inflammatory cytokines capable of initiating this cascade are consistently found to be increased in major depression, [15] as is the shift of tryptophan metabolism from serotonin to kynurenine formation, resulting in a high kynurenine/tryptophan ratio that is significantly associated with depression symptoms.[16] Elevated quinolinic acid accumulates in the brain tissue and has the potential to cause significant neuronal damage.[17] Magnetic resonance imaging (MRI) scans show structural brain grey matter abnormalities in major depression, bipolar disorder and schizophrenia.[18] Pro-inflammatory cytokines also increase serotonin transporter (SERT) activity (involved in recycling serotonin for reuse), thus further reducing overall serotonin activity.[19, 20]

A diet low in omega-3 or high in omega-6 intake results in increased pro-inflammatory cytokine production from AA (the long-chain omega-6 fatty acid responsible for the production of pro-inflammatory eicosanoids) and, consequently, pro-inflammatory cytokines must be balanced with the long-chain omega-3 fatty acid EPA, whose eicosanoids have the opposite effect. Direct supplementation with EPA significantly reduces the production of inflammatory cytokines, including TNF-α, IL-6, IL-2, all of which are elevated in depressed individuals.[21, 22]

The AA to EPA ratio therefore determines inflammatory regulation and also correlates with depression severity. Treatment with omega-3 results in an improvement in validated depression scores that further correlate with improved AA to EPA ratios. In addition to the AA to EPA ratio, the omega-3 index is also a reliable indicator of depression risk.[23] Originally developed as a biomarker of cardiovascular disease risk, the omega-3 index is the sum of EPA and DHA in red blood cell membranes, expressed as a percentage of total red blood cell fatty acids and accurately reflects tissue and organ concentrations, making it an excellent biomarker of long-term dietary omega-3 intake.[24] As such, the AA to EPA ratio and omega-3 index are important biomarkers of depression risk and severity – together with likelihood of omega-3 treatment response success. Ideally, the AA to EPA ratio should be no more than 3:1 and can be determined by the Opti-O-3® blood spot fatty acid biomarker test. Once a satisfactory AA to EPA ratio is achieved, optimising the omega-3 index to 28% will offer synergistic and long-term mental health benefits.

Interferon, a pro-inflammatory cytokine, is the only treatment for chronic hepatitis C infection. Treatment
is, however, associated with severe psychiatric symptoms, including depression.[25] Treating hepatitis C patients with IFN-α based immunotherapy causes immune activation and subsequent onset of depression.[26] Phospholipase A2 (PLA2) and cyclooxygenase 2 (COX2) are the two key enzymes involved in fatty acid metabolism pathways, which in turn play an important role in cytokine-induced depression. Genetic variations in the COX2 and PLA2 genes increase the risk of IFN-α induced depression, possibly by affecting the levels of EPA and DHA.[27] Omega-3 polyunsaturated fatty acid (PUFA) deficiency has been associated with an increased risk of IFN-induced depression. In a two-week, double-blind, placebo-controlled trial, Su and colleagues compared the capacity of EPA, DHA and placebo to prevent IFN-α-induced depression in 152 patients with chronic hepatitis C virus infection. EPA pre-treatment increased both EPA and DHA erythrocyte levels and was found to be effective in preventing IFN-α-induced depression, whereas the effects of DHA-only had modest effects that were not sustained.[28] NF-κB is a primary transcription factor involved in the synthesis and release of pro-inflammatory cytokines and is up-regulated in depressed patients. EPA has been shown to decrease NF-κB activity, with a corresponding decrease in the levels of numerous pro-inflammatory cytokines. DHA, in contrast, despite reducing NF-κB, appears to have a pro-inflammatory effect, increasing a number of pro-inflammatory cytokines including IFN-α, IL-6, and IL-15.[29] As DHA has previously been suggested to potentiate inflammation in conditions where inflammation is a key moderator, the use of DHA-free supplements may be most appropriate in the treatment of chronic inflammatory conditions.[30]

The mechanism of action of EPA in depression

EPA has numerous anti-inflammatory properties and the mechanisms of action of EPA in the treatment of depression are summarised in figure 3. EPA directly competes with AA, inhibits COX2 enzyme activity and reduces PGE2 synthesis, with favourable outcomes on pro-inflammatory cytokine production. Interestingly, a reduction in COX2 activity not only has a general anti-inflammatory action but also specifically down-regulates the IDO enzymes cascade and the production of potentially neuro-damaging metabolites.[19, 31] In addition to its role in the metabolism of PUFA, PLA2 is directly responsible for releasing omega-3 from the phospholipid backbone.[32] If replacement of omega-3 does not match the release, or if levels of PLA2 are high, then cell membranes can become depleted, leading to deficiencies.[33] By reducing the production of PLA2, EPA protects cell membrane integrity.[34] Throughout life, adequate supplies of omega-3 are crucial for maintaining the fluidity of neuronal membranes that are essential for the optimal functioning of membrane-bound and membrane-associated proteins, including neurotransmitters, neurotransmitter receptors and ion channels.[35, 36] EPA influences both the production and function of neurotransmitters known to play a role in the symptoms of depression, such as serotonin (involved in mood, emotion, sleep and appetite).[34] EPA also plays a key role as a ‘second messenger’ in neurotransmitter systems and modulates the activity of sodium, potassium and calcium ion channels that are required for the control of electrical impulses between nerve cells.[37]

As a potent anti-inflammatory, EPA plays a direct role in protecting the brain and nerves from dietary and/or stress-related damage. [37] The anti-inflammatory effect of EPA may occur indirectly via altering the expression of inflammatory genes, by down-regulating the production of inflammatory products derived from other fatty acids, or directly through the production of its own anti-inflammatory products.[38] It is through the regulatory influences on endocrine, cardiovascular and immune systems that these EPA derivatives exert profound influences on brain development and function.[39]

Nerve growth factors play an essential role in the plasticity and survival of the developed adult nervous system. Brain-derived neurotrophic factor (BDNF) is a neurotrophin that, in addition to regulating the survival, growth, and differentiation of neurons during
development, stimulates synaptic and cognitive plasticity in the adult brain. BDNF is an important biomarker for psychiatric conditions such as depression and bipolar disorder, with a direct correlation between omega-3 PUFA consumption and serum BDNF levels.[40] Levels of BDNF are known to be decreased in mood disorders and it is proposed that one of the neuroprotective roles attributed to omega-3 in mood disorders is via normalisation of BDNF levels [41, 42].

Supplements containing EPA ≥ 60% of total EPA + DHA, in a dose range of 200 to 2,200 mg/day of EPA in excess of DHA, are clinically effective against primary depression, with those studies using pure EPA at a dose of around 1g/daily the most efficacious. A 2013 study directly comparing EPA and DHA found 1g pure EPA to be significantly more effective than 1g DHA in treating depressive symptoms, thereby supporting the use of high concentration EPA, certainly in the initial treatment of depression.[45]

**Figure 3. EPA mechanisms in depression**

**Omega-3 EPA therapeutics for depression**

There is a strong relationship between alterations in the fat content of the diet and the manifestation of mood disorders, supported by epidemiological studies showing a clear correlation between fish consumption and prevalence of depression.[43] Fish type and cooking methods appear, however, to influence the potential antidepressant properties associated with fish consumption.[44] As such, the use of highly concentrated fish oil supplements as a method to increase omega-3 levels in compromised individuals offers therapeutic benefits not achievable by fish consumption alone.

Several major review papers and meta-analyses have [45-49] found that the ratio of EPA to DHA is of significance when establishing the efficacy of a supplement in the treatment of depression, and also for major depression with comorbid anxiety disorders. [50] The higher the EPA to DHA content, the greater the efficacy and for the duration of the initial ‘treatment’ phase, EPA has to be in excess of DHA to show benefits (figure 5).

Studies show that EPA is as effective as the most commonly prescribed antidepressants in the treatment of depression. The therapeutic effects of EPA, in terms of improving symptoms, are through the reduction of HPA-axis activity, which corresponds with a decrease in cortisol and inflammatory markers, and improved serotonin function.[34, 51] Whilst EPA isolate can be used effectively in combination with conventional antidepressants, the use of pure EPA as a standalone natural treatment has also been shown to be particularly effective in individuals who do not respond to conventional pharmaceutical medication.[52, 53] Furthermore, EPA offers a safe treatment option as it comes without the potential side-effects associated with common pharmaceuticals.

Using EPA in re-esterified triglyceride (rTG) form not only ensures delivery of highly concentrated EPA, but also optimises bioavailability, [54] key factors that have the potential to influence therapeutic outcomes.
Homocysteine and depression

Homocysteine is an intermediate sulphur-containing amino acid produced during the metabolism of methionine. Folate and vitamin B12 participate in the remethylation of homocysteine to methionine, which is subsequently converted to S-adenosylmethionine (SAMe) via methionine adenosyltransferase (MAT), a donor of methyl groups involved in the formation of neurotransmitters such as serotonin and dopamine. Deficiency in folate and B12 results in elevated serum homocysteine, which causes a decrease in SAMe, followed by impaired methylation and, consequently, impaired metabolism of neurotransmitters. In addition to its impact on neurotransmitter levels, elevated homocysteine also leads to increased oxidative stress and neurotoxicity, which may promote the development of various disorders, including depression.[55] In contrast, the transsulfuration pathway, an alternate pathway for homocysteine recycling, requires vitamin B6 (pyridoxal-5-phosphate) and the enzyme cystathionine-beta-synthase (CBS) to convert homocysteine to cystathionine – the intermediate product in the synthesis of cysteine, the amino acid which is then utilised to form the antioxidant glutathione. Low levels of glutathione or glutathione depletion is accompanied by a concomitant increase in oxidative stress and increased inflammation, which may play a role in the pathophysiology of diverse neuro-immune disorders, including depression.[56]

Fatty acids and homocysteine

In addition to folic acid, vitamin B6 and vitamin B12 deficiency, low levels of long-chain omega-3 polyunsaturated fatty acids can also lead to elevated homocysteine levels, [57] with high consumption associated with lower plasma homocysteine levels.[58] Omega-3 fatty acids are known to up-regulate the number of genes involved in homocysteine metabolism.[59]

The regulatory effect on gene expression by omega-3 therefore plays a direct role in the regulation of homocysteine levels and it is not surprising that deficiency of these important fats is associated with elevated homocysteine levels.[57] Whilst EPA is known to exhibit both antipsychotic and anti-depressive effects [60], it is not unreasonable to suggest that some of the benefits attributed to EPA in the treatment of depression occur via homocysteine regulation.
Recommended protocol for depression

The Opti-O-3 is a specialist fatty acid biomarker blood test that estimates the dose level of omega-3 required to raise red blood cell contents to predetermined levels and is based on two key influencing variables: an individual’s baseline omega-3 level and their body weight. [61] The Opti-O-3 profiling service can be used to identify bespoke omega-3 requirements based on a thorough fatty acid profile and measurement of key biomarkers:

- Omega-3 index: an early cardiovascular risk indicator
- Omega-6 to omega-3 ratio: an established marker of long-term health and chronic illness
- AA to EPA ratio: a measure of ‘silent’ or chronic inflammation

Taking into account body weight and red blood cell omega-3 levels, the final report recommends the specific dose needed to bring these biomarkers into healthy target ranges.

Pharmepa Restore and Maintain™ protocol

- Restores a healthy AA to EPA ratio
- Optimises the omega-3 index
- Reduces the production of pro-inflammatory products
- Increases the production of anti-inflammatory products
- Improves serotonin production and activity
- Improves sleep, cognitive function and immune response

Pharmepa RESTORE
Increases EPA and reduces the AA to EPA ratio for inflammation control (balances series 2 [AA] and series 3 [EPA] eicosanoids).

Pharmepa MAINTAIN
Introduces GLA for long-term maintenance of the AA to EPA ratio, with the addition of DHA for optimal support of the omega-3 index.

Homocysteine Control™
Vitamins B6, B12 & folic acid support homocysteine recycling for optimal neurotransmitter and glutathione production.

Homocysteine Control™ in conjunction with the Pharmepa Restore and Maintain™ protocol will help to:

- Lower homocysteine levels
- Support cardiovascular function
- Support a healthy mood
- Support methylation pathways
- Support neurotransmitter metabolism
- Support neurological function
References


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