Is depression a low-grade systemic inflammatory condition?

Dear Sir:

The conclusion of the recent meta-analysis by Appleton et al (1) that depression is more frequent in those whose intakes of long-chain polyunsaturated fatty acids (LCPUFAs), especially of n–3 fatty acids, are low suggests that depression could be a disorder of low-grade systemic inflammatory condition because LCPUFAs modulate proinflammatory events.

Recent studies showed that proinflammatory cytokines might cause depressive illness. This conclusion is based on the observations that 1) activation of the immune system and administration of endotoxin (lipopolysaccharide; LPS) or interleukin-1 (IL-1) to experimental animals induces sickness behavior that resembles depression (2); 2) activation of the immune system is observed in many depressed patients (3); 3) depression is more frequent in those with medical disorders associated with immune dysfunction (4); 4) treatment of patients with cytokines can produce symptoms of depression (4); 5) chronic treatment with antidepressants inhibits sickness behavior induced by LPS (5); 6) pro-inflammatory cytokines activate the hypothalamic-pituitary-adrenocortical axis (HPAA), which is activated in depressed patients (2); 7) cytokines activate cerebral noradrenergic systems, which is known to occur in depressed patients (4); and 8) several proinflammatory cytokines activate brain serotonergic systems, which have been implicated in major depressive illness and its treatment (6, 7). These results suggest that depression could be a low-grade systemic inflammatory condition.

The central nervous system regulates the production of the proinflammatory cytokines: tumor necrosis factor, IL-1, high mobility group-1, IL-6, and macrophage migration inhibitory factor through the efferent vagus nerve (8, 9). Acetylcholine, the principal vagal neurotransmitter, inhibits the production of proinflammatory cytokines through a mechanism dependent on the α7 nicotinic acetylcholine receptor subunit. Because vagal nerve stimulation (VNS) is of benefit in depression, I proposed that the beneficial effect of VNS in depression is due to its inhibitory action on the production of proinflammatory cytokines (10).

A significant decrease in n–3 fatty acids in plasma or in the membranes of red blood cells has been reported in subjects with depression (11–13). n–3 Fatty acids suppress the production of IL-1β, IL-2, IL-6, and TNF-α; therefore, n–3 fatty acids could play a major role in depression through their role in maintaining membrane fluidity, which influences neurotransmission, and in modulating the production of proinflammatory cytokines (14). In addition, antidepressants exhibit an immunoregulating effect by reducing the release of proinflammatory cytokines, by increasing the release of endogenous antagonists of proinflammatory cytokines such as IL-10 and, finally, by acting like inhibitors of cyclooxygenase (15). Double-blind placebo-controlled and other studies have shown that consumption of the n–3 fatty acids eicosapentaenoic acid and docosahexaenoic acid is associated with a longer period of remission in depressed patients (16–18). Thus, epidemiologic, experimental, and clinical data favor the idea that polyunsaturated fatty acids could play a role in the pathogenesis and treatment of depression. Well-planned larger trials with adequate power to detect clinically important benefits are required to determine the relevant dose of fatty acids to be used for the treatment of depression.

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REFERENCES


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Reply to UN Das

Dear Sir:

We thank Das for highlighting the potential role of inflammatory processes in depressive illness; however, this discussion is based on a misinterpretation of our recent meta-analysis (1). The meta-analysis concluded that there is very limited trial evidence currently available on the effects of n–3 long-chain polyunsaturated fatty acids (LCPUFAs) on depressed mood and that, because of the heterogeneity of this evidence, any conclusions concerning the benefits of n–3 LCPUFAs for depressed mood should be drawn with considerable caution.

Although previous biochemical studies, as reported in our article and elsewhere (2), have suggested that depression is more likely in those whose intake of n–3 LCPUFAs is low, information on n–3 LCPUFA intakes before supplementation was not given in our article. Furthermore, only 3 of the 18 trials detailed in our article were specifically conducted in individuals with low n–3 LCPUFA intakes before supplementation (3–5), and 2 of these trials showed no effects of n–3 LCPUFA supplementation on depressed mood (3, 4).

Second, although a meta-analysis of a limited number of trials that involved individuals with major depression suggests benefits, these trials were small and evidence of heterogeneity among them suggests that conclusions should be tentative. We do agree with Das on the need for well-planned larger trials with adequate power to detect clinically important effects, but, until such trials indicate a benefit, we do not advocate the use of n–3 LCPUFAs for the treatment of depression.

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