

PHOSPHATIDYLCHOLINE CONTAINING LONG CHAIN OMEGA-3 FATTY ACIDS: A TREATMENT ADJUNCT FOR PATIENTS WITH ANOREXIA NERVOSA?

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received: 12.12.2019;

revised: 7.2.2020;

accepted: 23.2.2020

SUMMARY

Background: Anorexia nervosa (AN) is a serious mental disorder with a high mortality rate and often a chronic course. In contrast to many other common mental disorders, there is no drug therapy approved for AN.

Methods: We performed a narrative literature review to consider whether a choline-containing molecule, such as phosphatidylcholine (PC), with an omega (ω)-3 long chain polyunsaturated fatty acid (LCPUFA) could be a potential future medicinal treatment for AN.

Results: Choline and LCPUFAs have individually shown benefit for mental health. Case series and pilot studies suggest ω -3 LCPUFAs may be effective in eating disorders. However, pharmacodynamic and pharmacokinetic considerations suggest a greater benefit from the combination of both components.

Conclusion: The combination of a choline-containing molecule with an ω -3 LCPUFA may be clinically effective and well tolerated. This idea is supported by the current literature on the role of inflammation, the microbiome, the gut-brain-axis, hormonal, neurotransmitter and intracellular signalling, and on the structure and fluidity of nerve cells membranes in patients with AN.

Key words: omega-3 fatty acids - choline - phosphatidylcholine - cytokines - anorexia nervosa

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INTRODUCTION

Anorexia Nervosa (AN) has one of the highest mortality rates of all psychiatric illnesses (Arcelus et al. 2011). It is defined by restricted calorie intake, malnutrition and body image disturbances (American Psychiatric Association 2013). Given that approximately 20% of AN patients become chronic sufferers (Steinhausen 2002), there is a need for novel and effective treatment options. We propose that the use of a choline-containing molecule, such as phosphatidylcholine (PC), with an omega (ω)-3 long chain polyunsaturated fatty acid (LCPUFA) may be a potential future treatment option for AN. Both of these molecules individually have beneficial effects on brain structure and function (Satogami et al. 2017), however a combination of these molecules is not yet commercially available.

POLYUNSATURATED FATTY ACIDS

Polyunsaturated fatty acids (PUFAs) are long hydrocarbon chains that are essential structural and signalling components of the phospholipids in human cells. Two classes of LCPUFAs, ω -3 fatty acids (FAs) and ω -6 FAs, are particularly important in regulating membrane

function (Das 2006) and make up a significant portion of the FAs in the brain (Calder 2016). ω 3-LCPUFAs cannot be produced by the human body and thus need to be consumed through our diet. The ω -3 FA group includes α -linoleic acid (ALA), which is commonly found in plant oils such as flaxseed, soybean and canola oil as well as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), both commonly found in marine oils such as fish, krill and squid oils, and some new algae and single cell sources. Major sources of ω -6 dietary sources include nuts and plant oils and there is a small amount of the ω -6 LCPUFA arachidonic acid (AA) in animal products. The ideal ω -6 to ω -3 ratio in the diet is unknown but is suggested to be somewhere between 2:1 and 4:1 (Simopoulos 2003). However, the estimated dietary ratio in the Western diet is in excess of 15:1 due to the high intake of ω -6-rich plant oils (Simopoulos 2003). A low ω -3 LCPUFA status has specifically been found in AN patients, as compared to controls (Caspar-Bauguil et al. 2012).

Choline was recognized as a dietary essential nutrient in 1998 and is required for the synthesis of acetylcholine, sphingomyelin and phosphatidylcholine (PC). It is also a major source of methyl groups (Blusztajn et al. 2017). Neurons have not been found to

synthesize choline and as such, the brain depends on diet and the endogenous synthesis for a supply of choline (Blusztajn et al. 2017). As choline has important metabolic functions, its deficiency has been hypothesized to contribute to non-alcoholic fatty liver disease, cardiovascular disease, and neurological and psychiatric disorders (Zeisel & da Costa 2009). De novo synthesis of choline occurs primarily in the liver by methylation of phosphatidylethanolamine (PE) to PC; however, this process does not meet human requirements. Therefore, a dietary source is also needed (Zeisel & da Costa 2009). Choline in the diet and body is found in a number of forms including the aqueous forms of free unesterified choline, phosphocholine and glycerophosphocholine (GPC) as well as the lipid-soluble molecules PC, lysophosphatidylcholine (lysoPC) and sphingomyelin (Zeisel et al. 2003). In a study of young pregnant women, it was found that PC was the major choline form consumed, contributing 48±2% of total intake (Lewis et al. 2014). PC is a choline containing a phospholipid with two FAs attached. Men and postmenopausal women are more susceptible to choline deficiency due to lower estrogen levels, which promotes de novo synthesis (Zeisel & Caudill 2010). In the healthy population, adolescent girls and young women would not usually be at risk of choline deficiency. However, in AN, disruption of estrogen synthesis together with a low intake of the foods that provide a source of choline in the diet would place these individuals at a similar risk to males. Currently, there is no evidence on which to base diet recommendations for the quantity of choline in the diet of AN patients.

When stimulated, the phospholipids (including PC) in the membrane release ω -3 and ω -6 LCPUFAs to form a number of bioactive eicosanoids (Calder 2015). The ω -6 derived eicosanoids have strong pro-inflammatory effects, whereas ω -3 derived eicosanoids have less inflammatory or anti-inflammatory effects (Calder 2017). The anti-inflammatory effects of ω -3 LCPUFAs may counteract the signalling of pro-inflammatory cytokines which have been suggested to play a pathophysiological role in AN (Dalton et al. 2018) by influencing the action of hormones and neurotransmitters in the three most important neurocircuits of appetite regulation: the self-regulatory, hedonic, and homeostatic systems (Himmerich & Treasure 2018). Thus, we believe that ω -3 LCPUFA treatment could be a promising candidate for investigation in the context of AN. Administered together with choline, ω -3 LCPUFA treatment might be even more effective.

POTENTIAL BENEFITS OF Ω -3 AND CHOLINE

ω -3 LCPUFAs exert their anti-inflammatory potential through several interactions. EPA and DHA can partly inhibit components of inflammation including leucocyte chemotaxis, adhesion molecule expression, leucocyte-endothelial adhesive interactions, and the

production of eicosanoids (Calder 2015). For these reasons, they have been hypothesized to be potential treatments for a wide range of psychiatric conditions (Prior & Galduróz 2012). Additionally, ω -3 LCPUFAs can induce the production of inflammation-resolving molecules e.g., resolvins, protectins, and maresins (Calder 2017). ω -3 LCPUFAs can also inhibit the activation of the pro-inflammatory transcription factor, nuclear factor (NF)- κ B, through activating the anti-inflammatory transcription factor peroxisome proliferator-activated receptor (PPAR)- γ , resulting in reduced expression of inflammatory genes. Furthermore, ω -3 LCPUFAs can exert their effects indirectly by counteracting the inflammatory ω -6 FAs (Calder 2017).

A body of research reports an association between gut microbiota dysbiosis and mental health (Iannone et al. 2019). ω -3 LCPUFAs have been shown to modulate the intestinal environment by altering the gut microbiota composition, leading to an increase in the population of bacterial taxa that promote eubiosis, rather than dysbiosis and inflammation (see Costantini et al. 2017 for a review). Furthermore, through their effects on the gut microbiota, ω -3 LCPUFAs have been found to influence the gut-brain axis (Sampson & Mazmanian, 2015), which plays an important role in mental health (Scriven et al. 2018). Both a lower ω -3 LCPUFA status (Caspar-Bauguil et al. 2012) and altered microbiome diversity (Seitz et al. 2019) has been implicated in AN.

Further to their anti-inflammatory potential, ω -3 LCPUFAs may be of relevance to AN patients through their other functions (see Shih et al. 2017 for a review). For example, Yehuda & Rabinovitz (2016) have postulated that the beneficial effects that ω -3 LCPUFAs have on AN patients may be due to their ability to stabilise the neuronal membrane fluidity index. It was recently suggested that the differential postprandial ω 6-derived eicosanoid shift that has been reported in those with AN might contribute to the food aversion that is typical of these patients (Shih et al. 2017). In support of this, LCPUFAs have been shown to increase appetite (Damsbo-Svendsen et al. 2013), enhance endocannabinoid-mediated neuronal functions (Lafourcade et al. 2011), and restore the disturbed blood-brain barrier functions (Yehuda et al. 2005).

Supplementation with choline has been studied in a number of neurological diseases in adults, including age-related memory and cognitive decline, Alzheimer's disease, epilepsy, and inherited conditions, such as Down and Rett syndromes, with promising results (for review see Blusztajn et al. 2017). These studies supplemented choline as a salt (free choline). There is, however, a lack of studies using PC as a treatment for brain disorders. A medication combining choline and ω -3 LCPUFAs is not yet commercially produced. However, hypothetically, PC could be synthesized to contain an ω -3 LCPUFA in at least one of the FA positions. It would be favourable to place this ω -3 LCPUFA in the sn-2 position as this has the potential to be absorbed and

transported across the blood brain barrier (Hachem et al. 2016). PC and ω -3 LCPUFAs have very few side effects. The most commonly reported are gastrointestinal disturbances, such as nausea, and a fishy aftertaste (when fish is the source of the ω -3 LCPUFAs). Given their mild nature, these side effects rarely influence patient adherence (Freeman et al. 2010, Akhondzadeh et al. 2013). Indeed, in AN samples, ω -3 LCPUFA supplementation has generally been reported to be acceptable and well-tolerated (Manos et al. 2018, Woo et al. 2017, Ayton et al. 2004).

CLINICAL RESEARCH IN AN

ω -3 LCPUFA supplementation in the context of AN is in its infancy and has therefore, only been examined in a few studies in AN specifically. In a randomized controlled trial (RCT) investigating EPA supplementation (480 ml, 620 kcal, 32 g protein \pm 2.2 g EPA) in cancer cachexia, a wasting syndrome that leads to weight loss like in AN, the use of EPA was found to ameliorate the loss of skeletal muscle mass exhibited by these patients (Fearon et al. 2003). In people with AN specifically, we identified one case series of seven adolescent patients supplemented with EPA (1 g/day E-EPA). The authors reported an increase in body weight and an improvement in anorexia psychopathology and depressive symptoms (Ayton et al. 2004). However, not all studies have been as promising. For example, in an RCT in adolescent girls with AN (n=53), there were no significant differences between supplementation with PUFAs (558 mg of eicosapentaenoic acid, 174 mg of docosahexaenoic acid and 60 mg of gamma linolenic acid) for 10 weeks during inpatient treatment, compared to placebo, in depressive and obsessive and compulsive symptoms (Pirog-Balcerzak et al. 2016). However, weight and ED symptom outcomes were not reported. Furthermore, Manos et al. (2018) conducted a small pilot RCT (n=24) in which adolescent girls with AN were supplemented with either 2,120 mg eicosapentaenoic acid/600 mg docosahexaenoic acid or placebo for 12 weeks, finding no difference in weight, eating disorder symptoms, or depression between the groups at the end of the intervention.

A high percentage of AN patients present with psychiatric co-morbidities, most notably depression (Ulfvebrand et al. 2015). Interestingly, Swenne et al. (Swenne et al. 2011) reported lower amounts of EPA and DHA in the erythrocyte membranes of adolescents presenting with EDs and depression, as compared to those presenting with only AN. In line with this, studies examining the effects of LCPUFAs on depressive symptoms (in patients both with and without AN) found that supplementation with EPA can decrease both inflammation and depressive symptoms (Rapaport et al. 2016, Peet & Horrobin 2002, Grosso et al. 2014, Jacka et al. 2013). Furthermore, adjunctive treatment with ω -3 LCPUFAs was found to augment the therapeutic efficacy

of fluoxetine (Jazayeri et al. 2008) and citalopram (Gertsik et al. 2012).

To our knowledge, choline or PC supplementation has not been studied in AN. There has been one animal study that suggested that dietary choline could stabilize brain function in rats with induced anorexia (Wöckel et al. 2007). Despite the limited evidence in AN, there have been a number of small clinical trials or cohort studies with patients with various weight-related and neurological disorders, such as obesity (see Edwards et al. 2019).

CONCLUSION AND FUTURE PERSPECTIVES

The use of a combination of choline and ω -3 LCPUFAs for the treatment of AN is a novel idea. Given the promising results for the use of either ω -3 LCPUFAs or choline in related illnesses, there is a clinical rationale for examining the combination of both nutrients as a treatment adjunct in patients with AN. These naturally derived, well-tolerated and low-cost agents could be a potential therapeutic tool for the treatment of AN, for which there are currently no approved pharmacological treatments available (Himmerich & Treasure 2018). We recommend the investigation of a novel PC molecule containing ω -3 LCPUFAs within RCTs, whose primary outcome measures should include weight changes, body composition changes (e.g., muscle mass, fat mass, etc), dietary intake, inflammatory marker changes, and general and AN-specific psychopathology as captured by the Eating Disorder Examination Questionnaire (EDE-Q, Fairburn & Beglin 2008). Additionally, recent genome-wide-association studies (GWAS) have shown genetic correlations of AN with schizophrenia, obsessive-compulsive disorder and depression (Cross-Disorder Group of the Psychiatric Genomics Consortium 2019, Himmerich et al. 2019). These correlations mirror the shared clinical symptoms between AN and these psychiatric disorders, such as overvalued ideas (body image disturbance), pseudo-hallucinations (the so-called anorexic voice), rituals, obsessions, and depressed mood (Himmerich & Treasure 2018). Thus, we would further recommend the use of questionnaires covering the symptoms of genetically- and clinically-related disorders such as the Brief Psychiatric Rating Scale (BPRS, Overall & Gorham 1962), the Yale-Brown Obsessive Compulsive Scale (Y-BOCS, Goodman et al. 1989) and the Depression Anxiety Stress Scales (DASS, Lovibond & Lovibond 1995).

We also suggest the involvement of patients in the design of these studies, along with the inclusion of patient-related outcomes and measures of experience and quality of life. A recent clinical audit revealed that patients want help with anxiety, concentration, sleep problems and anorexic thoughts (Dessain et al. 2019). Therefore, it would be of benefit to patients if these concerns were assessed in future RCTs. Such carefully

designed RCTs could provide an opportunity to explore the potential efficacy of choline and ω -3 LCPUFAs as a treatment modality in AN.

Relatedly, it would be of interest to explore the effects of these nutrients in the broader context of psychiatric disorders that frequently co-occur and share genetic risk factors with AN (Himmerich & Treasure 2018; Himmerich et al. 2019). For example, depression, anxiety, and PTSD, which are also associated with inflammation and brain structure abnormalities, may also benefit from potential treatments that combine choline and ω -3 LCPUFAs.

Acknowledgements:

Funding statement:

Theodoros Mavrogiannidis received Erasmus Plus funding via Aristotle University of Thessaloniki for a studentship at King's College London (KCL). Bethan Dalton is supported by a studentship awarded by the Department of Psychological Medicine, KCL and the Institute of Psychiatry, Psychology and Neuroscience (IoPPN), KCL. Hubertus Himmerich has received salary support from the NIHR BRC at the South London and Maudsley NHS Foundation Trust (SLaM) and KCL.

Conflict of interest: None to declare.

Contribution of individual authors:

Catherine J. Field & Hubertus Himmerich had the main scientific ideas which are the intellectual basis for this manuscript.

The first draft was written by Theodoros Mavrogiannidis.

Olivia Patsalos & Bethan Dalton revised this first draft substantially.

All authors discussed the manuscript and approved the final submitted version.

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