



A Possible Antidepressive Effect of Dietary Interventions: Emergent Findings and Research Challenges

Gilciane Ceolin, MSc^{1,2}

Vitor Breda, MD, MSc, PhD^{1,3}

Elena Koning, BScH, MSc¹

Arun Chinna Meyyappan, BScH¹

Fabiano A. Gomes, MD, PhD^{1,3}

Júlia Dubois Moreira, PhD⁴

Fernando Gerchman, MD, PhD^{5,6}

Elisa Brietzke, MD, MSc, PhD^{1,3,}*

Address

^{1,2}Centre for Neuroscience Studies (CNS), Queen's University, Kingston, 752 King Street West, Kingston, ON K7L 7X3, Canada
Email: elisa.brietzke@queensu.ca

²Postgraduate Program in Nutrition, Universidade Federal de Santa Catarina, Florianópolis, SC, Brazil

³Department of Psychiatry, Queen's University School of Medicine, Kingston, ON, Canada

⁴Department of Nutrition, Universidade Federal de Santa Catarina (UFSC), Florianópolis, SC, Brazil

⁵Endocrinology and Metabolism, Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, RS, Brazil

⁶Postgraduate Program in Medical Sciences: Endocrinology, Department of Internal Medicine, Faculty of Medicine, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil

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Abstract

Purpose Despite recent advancements in the treatment of depression, the prevalence of affected individuals continues to grow. The development of new strategies has been required and emerging evidence has linked a possible antidepressant effect with dietary interventions.

In this review, we discuss recent findings about the possible antidepressant effect of dietary interventions with an emphasis on the results of randomized controlled trials.

Recent findings A high consumption of refined sugars and saturated fat and a low dietary content of fruits and vegetables has been associated with the development of depression. There is evidence supporting a small to moderate beneficial effect of a Mediterranean-type diet in depression. In addition, new dietary protocols are being studied for their use as possible interventions, such as the ketogenic diet, Nordic diet, and plant-based diet.

Summary Lifestyle interventions surrounding diet and nutrition are a relatively affordable way to enhance response to treatment and to be employed as an adjunct in mental health care. Most studies, however, are limited by the difficulty in controlling for the placebo effect. Mediterranean-style diets seem to be the most promising as an adjunctive treatment for mood disorders. Larger randomized controlled trials that could assess predictors of response to dietary interventions are needed to establish a clear positive effect of diet and guide clinical care and nutritional recommendations concerning mental health care.

Introduction

Mood disorders, including major depressive disorder (MDD) and bipolar disorder (BD), are highly prevalent mental illnesses which affect mood, energy levels, sleep, and cognitive function [1]. Despite recent advancements in psychopharmacology, neuromodulation, and evidence-based psychotherapies, the treatment of mood disorders remains clinically challenging [2]. Most guidelines indicate symptomatic remission as the ultimate objective of the treatment of individuals with mood disorders, yet it is well known in clinical practice that most patients will deal with no response or residual symptoms [3, 4]. In addition, it is impossible to examine the limitations of antidepressant and mood-stabilizing treatments without considering that we are currently experiencing an event with catastrophic proportions: the Covid-19 pandemic. The long-term impact of Covid-19 on mental health remains to be established, but it is possible that mental disorders, especially depression, will become even more prevalent [5–7]. It will be imperative to absorb the personal, societal, and economic costs of mood disorder treatment in the post-pandemic world [8]. The significant burden of MDD and BD is extensively documented in multiple domains. Individuals with mood disorders experience a higher risk of death by suicide [9] despite relatively stable rates of suicide in past decades [10] and even recent decreases in suicide mortality in the USA [11]. However, suicide is not the

only important cause of mortality in individuals with mood disorders. Replicated evidence strongly indicates that individuals with mood disorders, especially BD, are disproportionately affected by metabolic conditions, including obesity, prediabetes and type 2 diabetes, and dyslipidemia [12, 13]. Similarly, it is likely that individuals with cancer, chronic pain, HIV, and neurological disorders such as multiple sclerosis and dementia will present with MDD during their lifetime [14]. The results of this particular combination of metabolic and mood symptoms contribute to increased morbidity, early mortality, treatment resistance, and the need for highly complex treatment approaches [15, 16]. Furthermore, improvements in medical care and life expectancy in the general population have not been reflected in individuals with severe mental illnesses and the mortality gap continues to increase [17, 18]. In addition to increased mortality and reduced life expectancy, individuals with mood disorders present with psychosocial impairment early in their illness with significant rates of disability and increased societal costs [19, 20].

The biological underpinnings for the association between mood disorders and metabolic abnormalities remain largely unknown. Notwithstanding, genome-wide association (GWAS) studies suggest a genetic basis for this association, with some genes contributing to increased vulnerability to both mood disorders

and obesity/metabolic syndrome [21]. In addition, both groups of conditions share environmental risk factors (e.g., exposure to adverse situations in childhood, substance use, and sleep deprivation) [22, 23]. The integration of genetic and environmental risk factors resulted in the contemporaneous causal paradigm in mood disorders in which MDD and BD are thought to result from the interaction between genes and environment during neurodevelopment [24, 25], which creates vulnerability for mood episodes [26, 27]. Interestingly, mood disorders have been associated with premature aging [28], with different studies demonstrating telomere shortening and epigenetic aging in mood disorders [29–31].

Among the factors involved in neurodevelopment and aging, nutrition has been considered a critical one [32]. The association between early life nutritional environment and risk for brain-based illness and poor

cognitive performance is well documented in studies involving various methodologies ranging from animal studies to large epidemiological cohorts [33–35]. However, only very recently has psychiatry focused on nutrition using more systematic approaches [36, 37]. Lifestyle modifications including physical exercises, smoking cessation, sleep hygiene, and dietary approaches are beginning to be cited in clinical practice guidelines as important initial interventions for individuals with mood disorders [14, 38]. The objective of this review is to discuss the emergent literature on the antidepressant effect of dietary interventions with an emphasis on the results of randomized controlled trials (RCT). As a rapidly evolving field, we also offer insight regarding current challenges and solutions for advancing the study of nutritional approaches in mood disorders.

Nutrition and health

The nutritional science is considered a recent field of research. Since the discovery of the first vitamin in 1926 until now, we have followed a growing development in particular effects of isolated nutrients and, more recently, specific diet patterns focused on complex non-communicable chronic diseases such as diabetes, cardiovascular disease, cancer, obesity, and mental health [39]. Following the evolutionary transition of industrialization, the introduction of daily intake of refined carbohydrate and saturated fat accompanied by low intake of fibers, fruits, and vegetables in modern Westernized societies was accompanied by the increase of overweight and obesity [40]. This pattern characterized as the Western Diet has been implicated in the main causes of morbidity and mortality due to chronic diseases in the USA and most Western countries [41].

On the other hand, some diet patterns such as the Mediterranean diet have been related with benefits such as cardiovascular health, reduction in the incidence of obesity, hypertension, metabolic syndrome, and better glycemic control [42]. This pattern is found in civilizations surrounding the Mediterranean Sea and is characterized by the intake of plant-based foods, nuts, olive oil, whole cereals, minimally processed and seasonally fresh foods, moderate intake of fish and poultry, and low intake of red meat [43]. The dietary approaches to stop hypertension (DASH) was based on studies aiming to decrease blood pressure funded by the National Institute of Health (NIH). This diet is based on foods rich in protein, fiber, potassium, magnesium, and calcium, such as fruits, vegetables, beans, nuts, whole grains, and low-fat dairy. It also limits foods high in saturated fat and sugar [44, 45]. Another diet, with extensive benefits for treatment resistant epilepsy in children, the ketogenic diet, has been studied as a possible intervention for depression and cognitive impairing conditions. The classic ketogenic diet consists of a

high-fat (90%) and low-protein/carbohydrate diet, with restricted calories and fluids. Nowadays, there are some variations to turn it into a more tolerable and palatable diet [46].

Dietary interventions as an emergent strategy in the treatment of mood disorders

Psychiatrists and other mental health professionals frequently receive questions from their patients about the potential benefit of lifestyle changes in the treatment of depression. If there is some controversy about the benefit of specific diets [47], little doubts remain about the deleterious impact of an unhealthy diet on mental health, particularly on depression [48•, 49]. Replicated evidence suggest that an unhealthy diet, characterized by the ingestion of significant amounts of processed food, refined grains, sugar, artificial additives, and a low content of fruits and vegetables, is associated not only with an increased risk of depressive symptoms in individuals who are otherwise healthy [50], but also with increased severity of depressive symptoms in individuals with mood disorders [48•]. A meta-analysis also evidenced an increased risk of depression related to the consumption of pro-inflammatory foods and Western diets by 45 years and older [48•]. Ecological studies support the notion that several different diets might be considered healthy from a population perspective. Studies with migrant populations confirm the harm of abandoning healthy dietetic habits from the original countries and adopting the Western diet [51], which is often accompanied by unhealthy weight gain [52]. It has been proposed that the consumption of unhealthy foods induces inflammation and may be one of the ways in which diet is related to mental health [53, 54].

Although some discussion in the literature about the antidepressant effect of dietary interventions still persists, in recent years, the results of observational and interventional studies, including RCTs, support a small to moderate therapeutic size effect of dietary interventions in MDD [55•, 56•]. The conduction of systematic assessments of the antidepressant effect of dietary interventions was crucial to control for potential confounders and to approximate studies with nutrition to the scientific rigor adopted in pharmacological interventions.

The most promising dietary intervention for the treatment of depression in clinical practice is a Mediterranean-style diet. So far, the results of two RCTs support the superiority of this dietetic approach in reducing the severity of depressive symptoms after 12 weeks when compared to control groups [57, 58]. Another study with a similar intervention but a shorter follow-up period (3 weeks) also found similar results [59]. Interestingly, a recent RCT compared the Mediterranean diet supplemented with dairy products to a low-fat diet, demonstrating improvements in mood and processing speed in adults aged 45 years or older with cardiovascular risk factors [60].

In the PREDIMED RCT (3 years of follow-up), a Mediterranean diet supplemented with extra-virgin olive oil ($n = 2543$) or nuts ($n = 2454$) was compared

with a low-fat diet ($n=2450$) in a community-dwelling high cardiovascular risk Hispanic population of men aged 55 to 80 years and women aged 60 to 80 years. Although a non-significant protection against depression was found with the Mediterranean diet, subgroup analysis subjects with diabetes receiving the Mediterranean diet and nuts (30 g per day of mixed nuts: 15 g walnuts, 7.5 g hazelnuts, and 7.5 g almonds) had a significant protection against the development of depression (adjusted HR=0.59; 95% CI 0.36 to 0.98) [61].

The Australian SMILES trial, a parallel-group single-blinded RCT of an adjunctive dietary intervention for depression, compared a diet support group ($n=31$) with a social support group as control ($n=25$). The diet support aimed to improve the dietary pattern towards a Mediterranean-style diet. After 12 weeks, the diet support had a significant improvement in depression symptoms measured by the Montgomery-Asberg Depression Rating Scale when compared to controls [$t(60.7)=4.38, p<0.001$, Cohen's $d=-1.16$] [57].

One of the key challenges with dietary interventions is their implementation, because of several barriers: low income, socio-cultural traditions, and taste-preferences. Low-income families are more exposed to dietary patterns considered unhealthy [62] and healthy diets are more expensive [63]. Those living in poverty are at a higher risk for mental disorders [64] and would potentially benefit more from dietetic interventions. Unfortunately, low-socioeconomic status is also associated with poor treatment adherence [65]. Among the studies we reviewed, the drop-out rates varied, but overall compliance with the diet was good, and participants were able to increase the consumption of prescribed foods. These preliminary data show that implementing dietary changes may result in significant improvements in affective symptoms and is feasible provided they are supported by dietitians, although the maintenance of a healthy diet in the long-term remains an obstacle in some instances.

In addition to the available data, several other studies are currently being conducted to evaluate the antidepressant effect of other diets [66]. For example, our group is currently conducting an open-label single-arm interventional study of 12 weeks of medically supervised ketogenic diet in individuals with MDD who did not properly respond to first-line antidepressants (Bambokian et al., submitted). The ketogenic diet is characterized by reduced carbohydrate content and high-fat consumption and subsequent use of ketone bodies as the primary energy source, reducing glucose use by the brain. This diet may have mood-stabilizing properties through altered excitatory/inhibitory status affecting the signaling of the neurotransmitters dopamine, GABA, and glutamate, as well as more effective ATP production with a reduction of reactive oxygen species production [66, 67]. Another study currently undergoing recruitment is a pilot RCT with 8 weeks of a healthy Nordic diet versus a control diet for individuals with MDD [68]. The Nordic diet consists of a high intake of vegetables and is associated with reduced inflammation and improved metabolic markers, insulin sensitivity, and cognition [68]. In addition, a multi-site RCT implemented the vegan diet for 18 weeks in which significant improvements in depressive symptoms were shown [69]. Plant-based eating seems to promote gut microbiome diversity and anti-inflammatory actions through greater consumption of plant fibers and proteins [70].

Discussion

Taken together, the results of the interventional trials, most notably RCTs, support an antidepressant effect of dietary interventions, especially those which are similar to the Mediterranean diet [57, 58, 71–73]. Notwithstanding, the results and the experience derived from the conduction of these studies also bring some interesting and novel topics to discussion.

First, several of them, more or less explicitly, consider that mood changes and metabolic abnormalities are part of the same syndrome, the so-called “metabolic-mood syndrome” [74, 75]. An example is the Multi-country cOllaborative project on the rOle of Diet, FOod-related behavior, and Obesity in the prevention of Depression (MOODFOOD). In this trial, a large community sample of 1025 overweight adults with depressive symptoms who are not currently experiencing a major depressive episode were randomly submitted to daily nutritional supplements or food-related behavioral activation with the objective to prevent depression [76]. Even without finding results that support the adoption of the interventions under investigation, this approach has become progressively more accepted [77]. On the other hand, traditional psychiatric treatments, such as neuromodulatory approaches, have been investigated to target both psychopathology and metabolic variables with some promising results [78].

It is important to consider that mood disorders display vast phenotypical heterogeneity, which may inform the application of nutritional interventions. For example, over 100 different loci have been associated with the risk of developing MDD, and genetic studies have identified mood disorder phenotypes based on a variety of risk factors [79, 80]. Altered neural activity and functional connectivity have even been associated with different risk factors for depression, such as childhood trauma [81]. Furthermore, appetite in individuals with mood disorders may present as increased or decreased which has been linked to different actions of neuroendocrine hormones and neurotransmitters [82]. A growing body of evidence suggests that the identification of mood disorder subtypes based on physiology rather than symptom profile is paramount to improving our understanding of the mechanisms underlying disordered mood.

Emerging projects aim to improve mood disorder characterization and treatment according to this heterogeneity in physiological disease correlates [83]. For example, the Research Domain Criteria (RDoC) project involves the conceptualization of mood disorders as a matrix of symptoms and their proposed biological underpinnings [84]. Opposed to the application of pharmacological interventions which is largely symptom-based, nutritional interventions may integrate with the RDoC to address certain aspects of mood disorder pathophysiology. For example, some authors postulate that metabolic and nutritional variables could be more strongly associated to some domains of the depressive psychopathology (e.g., anhedonia) than to the general depressive symptomatic expression [85]. Therefore, it may even become clear that some constructs (e.g., mood changes and metabolic imbalances) should be treated together. According to the RDoC, treatment

selection that considers phenotypic variability in mood disorders is a step towards improved patient care.

Second, as both depression and metabolic disturbances are multifactorial, there is a trend in the literature to design multimodal interventions, involving not only dietary protocols, but a combination of diet, physical exercise, and other lifestyle changes [86, 87]. A recent meta-analysis on lifestyle interventions targeting modifiable risk factors in young people (aged 12–25 years) found 14 RCTs, which together found a non-significant trend towards a protective effect [88]. However, only one of those studies were conducted in a clinical population [89]. From a meta-analysis with observational studies, a healthy lifestyle including high-quality diet and sufficient physical activity was associated with a 50% reduction in the risk of depressive symptoms [90].

A third point of progress is related to the possible mechanisms of action involved in the antidepressant effects of dietary interventions [37]. Findings from several lines of evidence, including animal studies, support the antioxidant and anti-inflammatory properties of some diets. As MDD has been considered a condition associated with oxidative stress and persistent low-grade inflammation, mitochondrial function, and immune system activity may be relevant targets for intervention [91]. Among the most recently identified mechanisms, investigations of gut-brain axis activity are contributing to a more advanced body of knowledge about the interaction between body health issues and mental health [92, 93]. There is some evidence that individuals with depression represent a population with specific bacterial enterotypes or have a reduction in the diversity of the gut microbiome [94, 95]. Although some studies targeting the microbiome adopt methods such as probiotic supplementation or fecal transplant, diet manipulation may also be a safe and affordable way to change the microbiome [96–99].

The most skeptical observers would likely remind us about the high rates of placebo effect in any study conducted with populations with depression, even more so in those including interventions that are difficult to blind. The placebo effect occurs with any intervention under investigation for depression, although it seems to be more dependent on the population and the study design than the intervention per se [100]. However, it is likely that individuals participating in studies with lifestyle interventions may be physically healthier, present with less severe illness, and have more motivation to implement dietary changes. Therefore, larger RCTs with a more diverse patient population are needed to fully evaluate the therapeutic efficacy of different dietary interventions. If proven safe and effective, nutritional interventions may be an important alternative for patients that are not agreeable to antidepressant treatment for personal reasons or that have concerns about side effects and/or long-term medication use [56•]. Finally, recent studies have shown that some depressive symptoms may respond differently to diverse treatments, further supporting a role for nutritional interventions [101, 102]. Future research on predictors of response to dietary interventions will help tailor treatment selection towards a more personalized approach [103].

Conclusion

Studies with interventions for depression based on nutritional approaches and lifestyle interventions with diet as an adjunctive treatment show promising results. According to the literature to date, we can state that high consumption of sugars and saturated fat, and low consumption of fruits and vegetables are associated with depression. The development of larger RCTs are needed to assess predictors of response to dietary interventions and to establish a clear positive effect of diet, therefore, guiding clinical care and nutritional recommendations for mental health care.

Author contribution

All authors contributed with the conception and elaboration of this article. The first draft of the manuscript was written by Elisa Brietzke and Gilciane Ceolin and all authors commented and edited the further version of the manuscript. All authors read and approved the final version.

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Declarations

Conflict of interest

Gilciane Ceolin declares that she has no conflict of interest. Vitor Breda declares that he has no conflict of interest. Elena Koning declares that she has no conflict of interest. Arun Chinna Meyyappan declares that he has no conflict of interest. Fabiano A. Gomes declares that he has support from the 2020 Brain and Behaviour Research Foundation (P&S Fund Young Investigator Award), the Canadian Menopause Society, SEAMO and Queen's Health Sciences, and received CME materials honoraria from AbbVie. Júlia Dubois Moreira declares that she has no conflict of interest. Fernando Gerchman declares that he has no conflict of interest. Elisa Brietzke declares that she has no conflict of interest.

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