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Depression and lifestyle: Focusing on nutrition, exercise, and their possible relevance to molecular mechanisms

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Accumulating evidence has suggested the important role of lifestyle factors in depressive disorder. This paper aimed to introduce and outline recent research on epidemiological and intervention studies on lifestyle-related factors in depressive disorder with a special focus on diet. Evidence on exercise, sleep. and related behaviors is also described. Here, findings from meta-analytic studies are emphasized and related studies by the author's research group are introduced. Dietary factors that increase the risk of the illness include energy overload, skipping breakfast, unhealthy diet styles such as Western diet, inflammation-prone diet, and high consumption of ultraprocessed food (UPF). Nutritional imbalances such as inadequate intake of protein, fish (Ω3 polyunsaturated fatty acids), vitamins (folate and vitamin D), and minerals (iron and zinc) increases the risk of depression. Poor oral hygiene, food allergy, addiction to alcohol, and smoking constitute risk factors. Sedentary lifestyle and increased screen time (e.g. video games and the internet) confer the risk of depression. Insomnia and disturbed sleep–wake rhythm are also involved in the pathogenesis of depression. There is accumulating evidence at the meta-analysis level for interventions to modify these lifestyle habits in the protection and treatment of depressive disorder. Main biological mechanisms of the link between lifestyle factors and depression include monoamine imbalance, inflammation, altered stress response, oxidative stress, and dysfunction of brain-derived neurotrophic factor, although other players such as insulin, leptin, and orexin also play a role. To increase resilience to modern stress and ameliorate depression through modification of lifestyle habits, a list of 30 recommendable interventions is presented.

Keywords: *depression, diet, exercise, lifestyle, sleep.*

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Depressive disorder is a serious psychiatric illness characterized by depressed mood, loss of interest and pleasure, altered appetite, disturbed sleep–wake rhythm, psychomotor retardation/agitation, fatigue, loss of concentration, self-reproach, and suicidal ideation.[1] The point prevalence of the illness was estimated at 4.4% worldwide.[2] Large-scale clinical trials such as STAR*D (Sequenced Treatment Alternatives to Relieve Depression) have demonstrated that a substantial proportion of patients with major depressive disorder (MDD) fail to respond to or achieve remission with the current first-line antidepressant therapy.[3] In addition, patients with MDD often show poor adherence to the current antidepressants due, at least in part, to their unpleasurable adverse effects, which requires additional treatment strategies.[4]

Depressive disorder is often triggered by stressful life events such as increased workload,[5] interpersonal relationship conflicts,[6] and other negative events.[7] However, the effects of such stress can be seen as a function of one's lifestyle, i.e. some people are more affected by such stressors, while others are more resilient and can deflect stress depending on their lifestyle habits, including diet, exercise, sleep, and coping with workload.[8] Indeed, a number of lifestyle habits are suggested to be associated with the risk of depressive disorder.[9]

In this regard, to modify or establish lifestyle to be more resilient to stress would be of clinical use in the treatment and protection of depressive disorder. This paper is a narrative review of studies of lifestyle factors associated with depressive disorder and those of modification therapies for the illness, focusing on diet, nutritional problems, and related habits. Here, special emphasis is placed on findings from meta-analytic studies and the author's own research.

Diet

Problematic dietary habits in modern society

Studies of dietary and nutritional issues associated with depressive disorder have revealed, mainly since the beginning of the 21st century, that, similar to other lifestyle diseases such as cardiovascular diseases and stroke, depressive disorder is strongly associated with dietary habits and nutritional status.[10] There are at least two nutritional problems in modern society: first is the excessive energy intake in the era of satiation, and second is nutritional imbalance due to the "Westernization" of food products and their intake, as food tends to lose micronutrients and polyphenols in the process of commercialization from natural ingredients into palatable foods. Both problems have been suggested to be associated with depression, as described below.

Excessive energy intake and depression

In recent years, the association between obesity and depression has been established wherein there seem to be shared biological mechanisms between the two conditions.[11,12] Accumulating evidence has indicated that there is a bidirectional association between depression and conditions such as obesity, diabetes, and metabolic syndrome, which are primarily caused by excessive energy intake. More than a decade ago, a meta-analysis of 15 longitudinal studies reported that obesity increased the risk of developing depression (odds ratio [OR], 1.55) and that depression increased the

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risk of developing obesity (OR, 1.58).[13] A more recent meta-analysis reported similar, albeit slightly attenuated, results; individuals with depression had an increased risk of being obese (relative risk [RR], 1.37), and those who were obese had an increased risk of being depressed (RR, 1.18),[14] suggesting that the strength of the association might be greater for the direction leading from depression.

In addition, obesity might be associated with clinical characteristics of depression. Toups et al.[15] at the University of Texas examined 662 patients with MDD and found that higher body mass index (BMI) was associated with greater medical illness, social phobia, and bulimia, whereas lower BMI was associated with more frequent posttraumatic stress disorder (PTSD) and drug abuse, which points to the possible importance of BMI in subtyping depression and its personalized treatment. Our research group found that patients with MDD who were obese (BMI ≥30 kg/m^2) had significantly more impairments than nonobese patients in cognitive functions such as working memory, fine motor speed, and executive function.[16] Magnetic resonance imaging (MRI) of the brain revealed that gray matter volume in cognition-relevant regions (the thalamus, temporal gyri, orbitofrontal, and inferior frontal gyri) were significantly reduced and that neural connections in the white matter (bilateral entorhinal and left optic radiations) were significantly more impaired in obese than nonobese patients, suggesting that obesity confers additional burden by affecting the brain and makes attaining functional recovery more difficult in patients.[16] A similar finding was obtained in patients with euthymic bipolar disorder by a different research group.[17]

The bidirectional association between type 2 diabetes and depression has also been established. A meta-analysis of studies from 1980 to 2002 already showed significantly increased prevalence of depression in patients with type 2 diabetes compared with those without (17.6% vs 9.8%; OR, 1.6).[18] A study investigating the complication rate of depression in Japanese patients with diabetes reported that 36.4% of 129 patients with ambulatory diabetes had depressive symptoms, and those with pain, microvascular disorders, and especially neuropathy had a higher incidence of depression.[19] In turn, a recent meta-analysis showed that depression puts patients at risk for future type 2 diabetes (RR, 1.18),[20] and another meta-analysis reported a bidirectional association between depressive symptoms and levels of hemoglobin A_{1c}.[21] According to a Japanese study, wherein 2764 men were followed up for 8 years, those who had depressive symptoms had a 2.3-fold higher risk of developing diabetes in the future than those who did not,[22] suggesting that the risk of diabetes seems to be relatively high in Japanese patients with depression presumably because physical activity–enhancing intervention has not been well introduced in Japan.

A meta-analysis of studies on metabolic syndrome also found that the syndrome increased the risk of depression (OR of 1.49 in nine cohort studies) and that depression increased the risk of metabolic syndrome (OR of 1.52 in four cohort studies).[23]

Importance of meal timing

An increasing number of studies have shown that meal timing is an important factor for mental as well as physical health. Wilson et al.[24] revealed that there are three patterns of meal timing: grazing (intake spread across the day), traditional (highest intakes reflected in breakfast, lunch, and dinner), and late (skipped/delayed breakfast with higher evening intakes). The late pattern was found to be associated with subsequent development of mood disorder, while the highly traditional pattern was associated with substantially lower risk of mood disorder, suggesting that nontraditional eating patterns, particularly skipping or delayed breakfast, are associated with mood disorders.[24] Our research group used the internet to obtain data on 11,876 Japanese individuals including 1000 with a history of depression, and examined the relationship between depression and lifestyle habits. We found that those who reported having ever been depressed were more likely to be obese or to have dyslipidemia and to snack and eat at night more frequently than those who did not.[25] It was also found that breakfast was consumed less frequently in the depression group, although the data were cross-sectional and thus preclude inference on causality.[25] Many studies including Japanese investigations have shown that skipping breakfast is often accompanied by having a late dinner (dinner within 2 h before bedtime) and bedtime snack (bedtime snack other than three regular meals), resulting in weight gain and subsequent overweight and obesity.[26–28] A meta-analysis of 45 studies showed increased risk of overweight/obesity (OR, 1.48 in 36 cross-sectional studies; RR, 1.44 in nine cohort studies) and abdominal obesity (OR, 1.31) in people with low-frequency breakfast intake per week versus those with high frequency.[29] Importantly, a recent meta-analysis of 14 previous studies including a total sample of 399,550 individuals demonstrated that there was a significant positive association between skipping breakfast and depression (OR, 1.39), stress (OR, 1.23) and psychological distress (OR, 1.55).[30] Although there was no significant association between skipping breakfast and anxiety in all age cohorts (OR, 1.31), a significant positive association with anxiety was found in adolescents (OR, 1.51).[30]

On the other hand, emerging evidence has shown that fasting interventions/habits, which inevitably skip breakfast and often result in calorie restriction, also have positive effects on metabolic indices and stress-related symptoms such as depression and anxiety.[31–34] One major modality of fasting is "intermittent fasting" (or "time-restricted eating"), which refers to patterns of fasting for 24 h or less, from 8 PM to noon, for example. A meta-analysis of six studies showed that intermittent fasting significantly reduces body weight (mean difference, −2.49 kg), BMI (mean difference, −1.56 kg/m^2), and related indices such as fat mass and waist circumference, compared with nonfasting.[31] A recent study reported that meta-analysis on eight randomized controlled trials (RCTs) showed a moderate and positive effect of intermittent fasting on depression scores when compared with control groups, although six non-RCTs found no significant evidence on anxiety or mood state.[32] We experienced a patient with gestational diabetes accompanied by mood dysregulation including depression who showed improvement in body weight, plasma glucose, and psychological distress after intermittent fasting.[33] Another meta-analysis reported that Ramadan fasting also has reducing effects on scores for stress, anxiety, and depression when compared with those before Ramadan, although Ramadan fasting is a religious habit and the effects may be explained by other factors (e.g. tobacco abstinence).[34]

Interventions for obesity and related conditions

Since there are bidirectional associations of depression with physical conditions due to excessive energy intake, it is likely that a negative spiral works between the two. Therefore, for patients who have depression combined with conditions such as obesity, metabolic syndrome, and diabetes, treating these physical conditions may help them break out of the negative spiral and thereby contribute to the improvement of depressive symptoms and cognitive impairments. Indeed, calorie restriction (a reduction in calorie intake by 30% to 40% without malnutrition) has been suggested to have antidepressant and antidepressant-like effects in humans and animals.[35–37] Also, a meta-analysis on 14 prospective studies showed that bariatric surgery is associated with long-term reductions (≥24 months) in anxiety and depressive symptoms in very obese people (≥35 BMI).[38] Two subsequent meta-analyses on the effect of bariatric surgery on depressive symptoms provided supportive results,[39,40] although there is a meta-analysis showing that postbariatric surgery depression is also common (approximately 15%).[41] In patients with diabetes (and possibly those with prediabetes), antidiabetic pharmacotherapy such as metformin and glucagon-like peptide-1 agonists seem to be effective in reducing depressive symptoms and cognitive impairments.[42,43] Guo et al.,[44] for example, conducted a clinical trial examining the effect of metformin in patients with MDD and type 2 diabetes, and found that metformin was associated with improved depression scores together with improved cognition, compared with placebo. Psychosocial interventions have also been suggested to be effective for depression in patients with diabetes in a meta-analysis.[45]

Notably, some antidepressants tend to cause weight gain, while others do not, and a meta-analysis reported that drugs such as mirtazapine, amitriptyline, and paroxetine have significant weight gain effects while bupropion tends to reduce weight in the maintenance therapy,[46] indicating that a patient's BMI might be an important factor in selecting which antidepressant to use. In line, using bupropion seems to be more effective in obese patients with MDD than nonobese patients.[47]

Diet style and depression

Research has focused on nutritional imbalances that may occur in the process of Westernization of the diet. The association of the Mediterranean diet (characterized by a high intake of fruits, vegetables, legumes, grains, fish, and olive oil; low intake of meat and dairy products; and moderate intake of alcohol), known as a healthy diet style in the West,[48] with the risk of depression has been studied. A meta-analysis of longitudinal studies found that individuals following a Mediterranean diet had a lower risk of depression than those following it the least (RR, 0.67).[49] Healthy diets, such as the Mediterranean diet, are generally less likely to cause chronic inflammation, and a "less inflammation-prone diet," as assessed by the Dietary Inflammation Index,[50] has also been reported to reduce the risk of depression (RR, 0.76).[49] Increasing of an inflammation-prone diet is related to the fact that modern dietary habits in developed countries have been shifting towards more increased consumption of UPFs (snacks, drinks, ready meals, and many other food products formulated mostly or entirely from substances extracted from foods or derived from food constituents),[51] and this is further facilitated by the outbreak of the coronavirus disease 2019 (COVID-19) and contributes to weight gain.[52] A recent meta-analysis showed that UPF consumption was associated with an increased risk of depression (RR, 1.28); every 10% increase in UPF consumption per daily calorie intake was associated with 11% higher risk of depression among adults.[53] In children and adolescent populations, a meta-analysis showed that increased consumption of junk foods is associated with depression (OR, 1.62 for comparison between the highest and the lowest category), stress (OR, 1.34), anxiety (OR, 1.24), sleep dissatisfaction (OR, 1.17), and happiness (OR, 0.83).[54] In this context, the International Society for Nutritional Psychiatry Research (ISNPR) recommends the following five dietary habits: (i) follow "traditional" dietary patterns, such as the Mediterranean, Norwegian, or Japanese diet; (ii) increase consumption of fruits, vegetables, legumes, whole grain cereals, nuts, and seeds; (iii) include a high consumption of foods rich in Ω3 polyunsaturated fatty acids (PUFA); (iv) replace unhealthy foods with wholesome nutritious foods; and (v) limit your intake of processed foods, "fast" foods, commercial bakery goods, and sweets.[55]

The Japanese traditional diet has also been considered to be healthy, since it contributes to the longer longevity of the Japanese population.[48] Although few studies have examined the relationship between diet style and depression in Japanese individuals, Nanri et al.[56] reported in an occupational setting that those who scored higher on the Healthy Japanese Food Pattern, characterized by a high intake of vegetables, fruits, soy products, mushrooms, and green tea, had significantly lower rates of having depressive symptoms.

Nutrients and depression

Ω3 PUFAs

Among Ω3 PUFAs, it is common for eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) to become deficient unless consumed from fish in humans. These nutrients have long been known to be effective in preventing cardiac events.[57] The risk of depression has also been found to be associated with low fish intake (RR, 0.83 between the highest vs lowest consumption) in a meta-analysis of 26 studies (a total of 150,278 individuals).[58] Blood Ω3 PUFA levels were found to be moderately lower in individuals with depression ($N = 648$) compared with controls ($N = 2670$) in a meta-analysis of 14 studies.[59] At least five meta-analytic studies reported the efficacy of EPA and DHA supplementation in patients with depression,[60–64] although the reported effect sizes were small and caution is required due to potential publication bias.[64,65] Regarding the dose, Sublette et al.[60] pointed out that supplements containing EPA ≥60% of total EPA + DHA, in a dose range of 200 to 2200 mg/d of EPA in excess of DHA, were effective against primary depression. Subsequently, the ISNPR provided research practice guidelines in the treatment of MDD where both pure EPA or an EPA/DHA combination (EPA/DHA) ratio >2 were considered effective, and the recommended dosages should be 1 to 2 g of net EPA daily, from either pure EPA or an EPA/DHA >2:1 formula.[66] Still, a meta-analysis by Liao et al.[63] reported effectiveness of a smaller dose of less than 1 g. Thus, further studies are required to determine the optimal usage of Ω3 PUFAs in the treatment of depression.

EPA and DHA therapy have been suggested to be effective not only in depression but also in various psychiatric disorders. Thus, the American Psychiatric Association recommends eating fish at least twice a week and taking EPA + DHA for mood disorders as well as impulse control disorders and psychotic disorders.[67] In line, our research group reported that patients with bipolar depression had lower plasma EPA and DHA concentrations than healthy individuals and that EPA, but not DHA, concentrations were inversely correlated with plasma concentrations of the inflammatory cytokines interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α),[68] which supports the anti-inflammatory effects of EPA and suggests its importance relative to DHA in the treatment of inflammatory conditions. We also found that the symptom score of PTSD was negatively correlated with blood concentrations of EPA and fish intake in female residents ($N = 563$) of Kitaibaraki City hit by the tsunami in the Great East Japan earthquake,[69] suggesting the protective effect of EPA against PTSD. A similar result was obtained in Croatian war veterans.[70]

Vitamins

Among vitamins, folate and vitamin D, in particular, have been shown to be related to the risk of depression. It has repeatedly been reported that low folate concentrations in the serum and red blood cells increase the risk of depression, which was supported by a meta-analysis of 43 studies demonstrating lower folate levels in individuals with depression ($N = 8519$) compared with controls ($N = 27{,}282$).[71] Data from a Japanese occupational setting ($N = 530$), where 36% of the workers had depressive symptoms, showed that the percentage of people with depressive symptoms was higher in those with the lowest quartile of serum folate, compared with the remaining quartiles.[72] Regarding the effects of folate replacement therapy, some studies reported its efficacy for patients with depression treated with antidepressants.[73,74] However, the meta-analysis of four previous studies did not support its efficacy,[62] mainly because a single study with a very large sample size ($N = 475$) reported a negative result.[75] In contrast, a recent meta-analysis of nine studies ($N = 6707$ patients) showed that adjunctive L-methylfolate, an active form of folate, may have modest efficacy in antidepressant-treated adults with MDD.[76] Given that folate preparations are used to treat folate deficiency in daily clinical practice, the current author would recommend to measure folate levels and provide supplements for patients with depression who have such a deficiency. Folate is abundant in leafy vegetables, dietary liver, and soy products, and encouraging the intake of such foods would also be clinically useful.

Blood concentrations of B group vitamins other than folate should be checked and supplements should be provided if deficient, such as in patients with depression who have severe loss of appetite and/or excessive alcohol intake. In a Korean national cross-sectional study, a significant association was found between inadequate thiamine (vitamin B1) intake and depression.[77] Anecdotal cases of thiamine deficiency resulting in Wernicke encephalopathy, caused by a marked decrease in appetite and food intake due to the onset of a depressive disorder, have been reported.[78]

Vitamin D is produced by ultraviolet irradiation to 7-dehydrocholesterol in the skin, and in food, it is abundant in fish and mushrooms. It promotes calcium and phosphorus absorption in the small intestine and kidneys and promotes bone and tooth formation. Therefore, its deficiency can lead to osteomalacia and osteoporosis in adults. Blood vitamin D (25-hydroxy vitamin D) levels of ≥30 μg/L, 20 μg/L to 30 μg/L, and <20 μg/L are considered to be sufficient, inadequate, and deficient, respectively, to prevent osteoporosis.[79] Evidence is also accumulating for an association with depression, and a meta-analysis of previous studies examining blood vitamin D levels suggests that patients with depression have lower vitamin D levels than healthy individuals.[80] In line, data from a Japanese occupational setting reported that the group with a vitamin D level of ≥20 μg/L had a significantly lower frequency of depressive symptoms (OR, 0.6–0.8) than the group that with a level <20 μg/L.[81] On the other hand, however, a recent large RCT (25,871 adults in the United States) found no significant preventive effect of vitamin D against depression.[82] Further, a meta-analysis of 10 RCTs involving 1,393 participants failed to find a significant effect of oral vitamin D in the treatment of depression[83]; however, this meta-analysis was hampered by including studies on miscellaneous participants. In contrast, two relatively rigorous studies both reported positive results in augmentation of antidepressant treatment.[84,85] Further, vitamin D was found to be effective in an RCT comparing vitamin D and placebo (i.e. not used as augmentation of an antidepressant) in Iranian patients with MDD.[86]

Since human vitamin D levels show marked seasonal fluctuations due to seasonal variation in the strength of sunlight particularly in the high latitude areas, it is possible that vitamin D deficiency due to reduced daylight hours during the winter and early spring months plays an important role in the pathogenesis of seasonal depression; however, this hypothesis is yet to be proven and evidence is not convincing as to the use of vitamin D in the treatment of seasonal depressive disorder,[87,88] although some early papers reported the efficacy of vitamin D replacement therapy for seasonal depression and mood-enhancing effect in healthy individuals during winter.[89,90]

Taken together, further studies are required to conclude whether vitamin D is useful in the treatment of depression, particularly for those who have a deficient level of the vitamin. However, given that the majority of people have vitamin D levels within the inadequate or deficient range, levels of 25-hydroxy vitamin D should be checked for patients with depression, and replacement therapy should be considered particularly for those who are in the deficient range.

Amino acids

In a study of blood amino acid concentrations in patients with depression and healthy individuals, our research group found that levels of tryptophan, phenylalanine, tyrosine, and methionine were significantly decreased, while those of glutamate were increased, in patients with MDD compared with healthy controls.[91] Among these amino acids, tryptophan, phenylalanine, tyrosine, and methionine are all essential amino acids and must be obtained from the diet. Further, these amino acids are the raw material for monoamines such as serotonin, dopamine, and noradrenaline (Fig. 1).[92] Although glutamate is not an essential amino acid, it is a neurotransmitter itself in the nervous system. The observation of reduced essential amino acids in patients with MDD leads to a hypothesis that adequately high protein intake may protect against depression. Although there seems to be a dearth of studies examining such possibility, data from the US National Health and Nutrition Examination Survey (2007–2014) including a total of 17,845 individuals 18 years or older showed that total protein intake was inversely associated with the risk of depressive symptoms (OR, 0.34 for quartile 4 vs quartile 1 of total protein intake).[93]

For individual amino acids, tryptophan might be of particular concern, since it has long been noted that tryptophan depletion can cause depressed mood in individuals with a history of depression and those predisposed to the illness.[94] There are many reports of lower blood tryptophan concentrations in patients with depression than in healthy controls, and this was confirmed by our meta-analysis.[95] Based on the early tryptophan depletion theory, several RCTs had already been conducted until 2000 using tryptophan as antidepressant augmentation therapy; four of seven studies yielded a positive result and one study using 5-hydroxy tryptamine reported a positive result. Together with the paucity of recent evidence, further studies are required to draw any conclusion.[62]

The observed decrease in phenylalanine and tyrosine is also interesting in that these are the material for production of dopamine and noradrenaline. This reduction in peripheral blood may be related to our observation and meta-analyses that the level of a metabolite (homovanillic acid) of dopamine, which is produced from phenylalanine through tyrosine (Fig. 1), was decreased in the cerebrospinal fluid (CSF) of patients with depression, compared with that of controls.[96–98]

Methionine is the starting point of the methylation cycle, and the active form of methionine, S-adenosylmethionine (SAM-e), donates the methyl group in the cycle. There is evidence based on a meta-analysis that SAM-e has antidepressant effects.[62] However, a more recent RCT in a relatively large sample ($N = 107$) of patients with nonremitted MDD failed to obtain evidence for its efficacy as an adjunctive agent to antidepressants.[99] Nonetheless, in Europe, SAM-e is used as a prescription drug, and, in North America, it is an over-the-counter drug.

Theanine is a unique amino acid that is abundantly contained in green tea (Camellia sinensis). It is a glutamate-derivative, which seems to have a partial antagonistic action against N-methyl-D-aspartate (NMDA) glutamate receptor.[100] Several clinical and preclinical studies

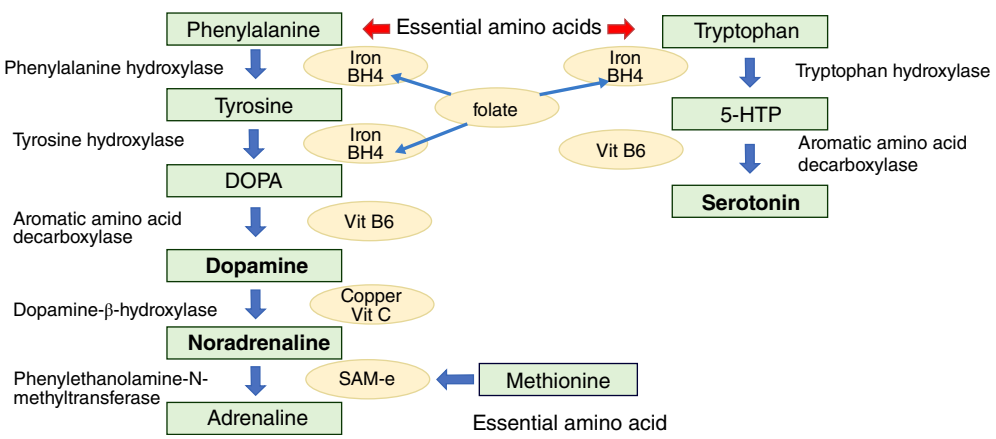

Fig. 1 Biosynthesis of monoamine neurotransmitters requires essential amino acids and micronutrients. This diagram shows enzymes and cofactors (described in the ovals) in the biosynthesis steps from essential amino acids to produce dopamine, noradrenaline, and serotonin (made by the author according to Nestler *et al*[92]). Folate is involved in stabilization and production of tetrahydrobiopterin (BH4) (see text). DOPA, dihydroxyphenylalanine; 5-HTTP, 5-hydroxytryptamine; SAM-e, S-adenosylmethionine; Vit, vitamin.

including ours have reported its relaxing effect, antidepressant (-like) action and enhancing effect of sleep quality.[100–103] Theanine is abundantly contained in high-quality green teas such as gyokuro and matcha (approximately 30 mg in one cup) and is also available as a supplement in the form of pills.

Minerals

Iron deficiency is common, particularly in women of reproductive age. For example, iron deficiency anemia (IDA) among women between the ages of 20 and 44 years in Shanghai and Tokyo were 14.8% and 11.4%, respectively.[104] Iron is necessary for the enzymes involved in dopamine production (Fig. 1) and metabolism, and its deficiency is thought to impair dopamine function. This possibility is indirectly demonstrated by the fact that patients with restless legs syndrome (RLS), characterized by an uncomfortable urge to move the legs while at rest, relief upon movement, and worsened symptom severity at night, often show low iron storage as expressed as low ferritin levels and that dopamine agonists are effective in the treatment of the syndrome.[105] Notably, in a sample of 549 untreated patients with RLS and 549 matched controls, the frequency of depressive symptoms (32.5%) and suicidal thoughts (28%) was 10-fold and three-fold higher, respectively, in patients with RLS than controls.[106] Consistent with this fact, symptoms of iron deficiency are known to produce depression-like symptoms such as fatigue, agitation, apathy, and poor concentration. In our analysis of a large internet survey, an association was found between iron deficiency anemia and a history of depression and stress symptoms.[107] Further, some reports suggest that mothers who had iron deficiency anemia or depletion of iron stores after giving birth to their children had an increased risk of postpartum depression compared with those who were not anemic (reviewed in Wassef et al.[108]). Albacar et al.,[109] for example, reported that ferritin levels 48 h after giving birth were found to be strongly associated with postpartum depression. Based on these findings, checking serum iron and ferritin levels for potential iron deficiency and treating with iron supplements would be effective in improving depressive symptoms. However, care should be taken not to overdose on iron, as excessive administration of iron tends to cause oxidative stress, increased blood viscosity, and impaired systemic response to inflammation and infection, which may pose a risk for various diseases.[110]

The possible role of zinc deficiency in depression was pointed out more than 2 decades ago.[111] Food additives often contain phosphorus, which inhibits the absorption of zinc; therefore, modern people are prone to having excess phosphorus while being deficient in zinc. In fact, approximately 30% of Japanese people were estimated to have dietary zinc below the required daily amount.[112] There have been many studies from several countries measuring peripheral blood zinc levels in individuals with depression in comparison with individuals without depression, and a meta-analysis on 17 studies (1,643 patients with depression and 804 controls) reported that zinc concentrations were approximately −1.85 μmol/L lower in patients with depression than in controls.[113] Animal studies suggest an antidepressant-like effect of zinc such that it decreased immobility time in forced swim tests.[111] Although human clinical studies are still scarce, a meta-analysis on five previous studies suggests its efficacy as supplements given in addition to regular antidepressants.[114] These results indicate that clinicians should measure zinc levels and replacement therapy should be given for patients with depression who have inadequate levels of zinc (<80 μg/dL).[115] Zinc preparations have been increasingly used for its deficiency in the clinical setting. In addition, providing nutritional guidance to encourage the consumption of a zinc-rich diet such as oysters, eel, and beef may also be effective.

An association between magnesium and depression has also been noted. A study of 5,708 members of the general population in Norway found that the lower the magnesium intake estimated by a dietary survey, the higher the depressive symptoms.[116] Magnesium is abundant in soy products, unrefined seeds and grains, and seaweed. However, it should be noted that it is lost through refining.

Dietary fiber

Dietary fiber is abundantly contained in whole grains, legumes, vegetables, and fruits. Consumption of dietary fiber promote the growth of beneficial microbes such as *Bifidobacterium* and *Lactobacillus*,[117] and has a variety of health benefits such as weight management, protection against constipation, irritable bowel syndrome (IBS), cardiovascular disease, type 2 diabetes, metabolic syndrome, and colorectal and lung cancers, to name a few.[118,119] However, the mean daily dietary fiber intake in Japanese markedly reduced in the latter half of the past century, i.e. 20.5 g/day in 1952, which rapidly declined to about 70% of the 1952 level in 1970, and thereafter there was little change.[120] There are not many studies examining the relationship between dietary fiber intake and depression; however, a meta-analysis of four case-control studies revealed that the consumption of dietary fiber in patients with depression was significantly lower, when compared with healthy controls. The same paper demonstrated that a higher dietary consumption of fiber was associated with significantly lower odds of depression (OR, 0.76).[121]

Tea, coffee, and other beverages

A meta-analysis of 15 observational studies (nine cross-sectional studies and six prospective studies) of beverage consumption and depression, including 20,572 cases of depression among 347,691 participants, showed that high consumption of coffee (RR, 0.73) and tea (RR, 0.71) reduced the risk of depression, while high consumption of soft drinks increased the risk (RR, 1.36).[122] The possible relationship between green tea consumption and depression has been investigated in Japan. Our research group found that patients with MDD consumed green tea less frequently than healthy individuals.[123] This cannot be explained by a decrease in water consumption by patients with depression, since they consumed more juices and other sweetened beverages than healthy individuals, which is consistent with the meta-analysis.[122] There are also reports from a Japanese occupational setting showing that higher green tea consumption was associated with decreased rate of depressive symptoms.[124] These Japanese groups also showed an association between lower coffee consumption and higher rates of depression.[123,124]

Herbs

There are many herbs that may be beneficial for depression.[125] Among them St John's wort (*Hypericum perforatum*) has long been well known as an antidepressant herb, and evidence of its efficacy for mild to moderate depression has been established.[126] It is used universally as a supplement in many countries, and, in Germany, physicians prescribe it as a medicine. It is also considered to be safe, although its concomitant use with other drugs requires caution because of interactions with various drugs. Concerning other herbal medicine, see the reviews, including that by Dai et al.[125]).

Alcohol

According to a meta-analysis on cohort studies looking at alcohol consumption and subsequent depressive symptoms, people with an alcohol use disorder were found to be at risk for depressive symptoms, while other status, even drinking a large amount daily, were not significantly associated with the risk.[127] It is possible that a modest amount of alcohol consumption may even reduce the risk of developing depressive symptoms, although this is still a matter of debate.[128] In principle, however, alcohol should be prohibited for patients who are currently treated for depression. The reasons for this are that it interacts with therapeutic drugs, and alcohol dependence may develop while relying on alcohol. Suicidal behavior and accidents are likely to occur due to a decreased level of consciousness and impaired judgment due to alcohol, and alcohol consumption before bedtime decreases the quality of sleep.

Probiotics

In recent years, a link between various diseases and gut microbiota has been noted, and the relationship between the intestinal environment and psychiatric diseases has also been studied.[129,130] In this context, probiotics (live microorganisms and food containing them that have a positive effect on the human body; fermented foods such as *Lactobacillus* and *Bifidobacterium*-involving beverages and yogurt) have been suggested to alleviate stress-induced depression-like behaviors and associated changes in the brain.[131] Although evidence on intestinal bacteria in patients with depression is still scarce, our research group found that patients with MDD had decreased levels of *Lactobacillus* and *Bifidobacterium*, compared with controls.[132] Although such a difference was not found in patients with bipolar disorder, *Bifidobacterium* levels were negatively correlated with blood cortisol levels, a stress hormone, and *Lactobacillus* bacterial levels were negatively correlated with sleep disturbance scores, suggesting a link of these bacteria with stress and sleep.[133] A more recent study of the author's and colleagues found that better outcomes of MDD were associated with an abundance of *Actinobacteria* and *Bifidobacterium* throughout the treatment period.[134]

Recently, results of clinical trials showing the efficacy of probiotics for stress symptoms and depression have been reported, and despite some negative reports, improvement of the intestinal environment is also thought to play an important role in patients with depression.[131] In addition, many patients with depression have IBS, which presents with chronic abdominal pain, diarrhea, and constipation of unknown cause (approximately 30% in the authors' cases above [Aizawa et al.[132]]). Since the efficacy of probiotics on IBS has been demonstrated by multiple meta-analytic studies,[135,136] for these cases, in particular, probiotics and fermented food containing beneficial microbes should be utilized and recommended.

Food allergy

Thus far, little is known about the role of food allergy in the pathogenesis of depression. Based on the link between inflammation in the gut and depression, our research group examined the possible association between depression and food allergy using a large number of data obtained from the internet, and reported for the first time that there is a significant association between the two in a dose-dependent manner, i.e. the more the number of food allergens, the more the risk of depression increases.[137] We subsequently obtained evidence that food allergy was associated with impaired quality of life (QOL) and sleep in psychiatric patients such as those with schizophrenia or mood disorders.[138] Thus, avoiding exposure to allergenic foods may be effective in ameliorating and/or protecting against depression and improving QOL and sleep.

Oral hygiene

A meta-analysis on the relationship of anxiety and depression with dental decay revealed that these psychiatric conditions were both associated with increased number of decayed, missing, and filled teeth or surfaces, although there was no association with periodontal disease.[139] A more recent meta-analysis, however, found that depression increased the odds of dental caries (OR, 1.27), tooth loss (OR, 1.31), and edentulism (OR, 1.17).[140] When the oral diseases were tested as an independent variable and depression as an outcome, associations with both edentulism (OR, 1.28) and periodontal disease (OR, 1.73) were found. These results again point to the possible bidirectional associations between depression and oral health.

Smoking

It is well known that many patients with mental illness, not just depression, are smokers. However, there has been some discussion on whether the high prevalence of smoking among patients with depression is due to the fact that smoking increases the risk of depression or whether smoking is a form of self-medication as a result of developing depression. Nicotine in cigarettes stimulates the release of dopamine and beta-endorphin, which, in turn, stimulates the brain's reward system and also promotes the secretion of adrenaline from the adrenal medulla, which has been shown to at least temporarily reduce depressive mood and improve cognitive function.[141,142] However, it is well known that cigarettes have toxic effects such as oxidative stress due to the large amount of free radicals contained in the smoke. A pooled analysis of the results of six studies reported a 1.7-fold increased risk of depression with smoking[143]; in the same paper, an analysis of the results of 12 studies reported that depression increases the risk of smoking by 1.4 times. Hence, there is a bidirectional association between smoking and depression. A recent analysis of UK Biobank data (approximately 460,000 individuals) using Mendelian randomized study methods also showed a bidirectional association, with smoking increasing the risk of depression by approximately two-fold and depression also increasing smoking rates.[144] Several other studies have also reported that smoking increases the risk of depression.[145,146] Given these findings, cessation of smoking should be recommended to smokers, and smoking cessation outpatient clinics should be considered when necessary.

Exercise

It has been pointed out that the decrease in people's physical activity and exercise and resultant sedentary lifestyle due to the development of the automobile society and industry is also a factor in the onset of depression. According to the 2017 National Health and Nutrition Survey (NHNS) in Japanese, during the 10-year period from 2007 to 2017,[147] the number of steps for men decreased from 7321 to 6846 steps per day and that for women decreased from 6267 to 5867 steps per day. However, the proportion of Japanese people who have an exercise habit (exercise for ≥30 min per session, at least twice a week, for at least 1 year) remains low at 10% to 30% among men in their 20s to 50s and 10% to 20% among women in their 20s to 50s (2017 NHNS).[147] The spread of COVID-19 has been further prompting people to work at home and refrain from unnecessary outings, and the lack of exercise is becoming even more serious.

Physical activity and exercise protect against depression

Accumulating evidence has suggested that people who are less physically active and exercise less have a higher risk of developing depression later in life. For example, a study in the 1990s in an approximately 25-year observation of 10,201 college graduates in the United States has already reported that the incidence of depression among those who were more physically active or who were athletes at graduation was lower than that among those who were less physically active.[148] A longitudinal study of 33,908 adults followed up for 11 years also reported that exercise in leisure time once a week reduced the risk of depression.[149] A recent meta-analysis on 15 studies comprising 191,130 participants showed an inverse curvilinear dose–response association between physical activity and depression, with steeper association gradients at lower activity volumes.[150] Relative to adults not reporting any activity, those accumulating half the recommended volume of physical activity (4.4 marginal metabolic equivalent task hours per week) had 18% lower risk of depression.[150] These findings clearly indicate that daily physical activity habits protect against the development of depression.

Efficacy of exercise therapy

Exercise has also been noted as an effective treatment for depression. In a 16-week RCT, Blumenthal et al.[151] compared groups treated with exercise therapy (either under a trainer or at home) with a group treated with antidepressant medication (sertraline) and a group treated with a placebo (sham medication). The two exercise therapy groups and the antidepressant treatment group had higher rates of remission of depression than the placebo group, and the effects of exercise therapy and antidepressants were similar. The effects of the group that received exercise therapy under a trainer and the group that received

exercise therapy at home were almost the same. It has also been reported that when comparing recurrence rates 10 months after depression that improved with exercise therapy and antidepressants, those who continued exercise therapy at home reported significantly lower recurrence rates than that of the group that continued medication.[152] There have been many other studies on the effect of exercise on depression, and a meta-analysis of 23 previous RCTs (total 977 participants)[153] has reported its significant efficacy. A more recent meta-analysis reported that multimodal exercise had the highest probability of being the most efficient exercise for relieving depressive symptoms.[154]

The European Psychiatric Association guidance on physical activity indicates that physical activity can improve depressive symptoms versus control conditions, with effects comparable to those of antidepressants and psychotherapy.[155] Physical activity can also improve cardiorespiratory fitness and QOL in people with MDD, although the impact on physical health outcomes was limited. For MDD, larger effect sizes were seen when physical activity was delivered at moderate to vigorous intensity and supervised by an exercise specialist.[155]

The exercise regimen includes walking or jogging (30–40 min per session, often in a group setting) or aerobics or dancing (20 min to 1 h per session) two to five times a week. However, many patients with depression cannot be instructed to walk for more than 30 min right from the beginning. Initially, it is advisable to start with walking for 5 to 10 min at a time. The length of time can then be increased gradually (e.g. by 5 min each week) and eventually to 30 to 40 min continuously, and faster walking can also be incorporated thereafter (e.g. Blumenthal et al.[156]). Resistance training should also be included, given that it is effective to improve depression and QOL as well as muscle strength.[157,158]

Exposure to Nature

The current rapid urbanization worldwide raises the problem of difficulty in exposure to nature (green and blue spaces) in urban life, which may be related to mental health problems.[159] The term green spaces refers to vegetation (e.g. trees, forest, garden, and jungle), whereas blue spaces are all the visible surface waters in space (e.g. lakes, rivers, and coastal water). One study, for example, reported that access to major green spaces was associated with self-reported history of depression (OR, 0.18),[160] and even view of green spaces from home was found to be associated with lower anxiety and depression.[161] Data from an 18-country survey ($n = 16{,}307$) revealed that frequency of recreational visits to green, inland-blue, and coastal-blue spaces in the past 4 weeks were all positively associated with positive well-being and negatively associated with mental distress.[162] If contact with green spaces has a positive effect on mental health, then gardening, which is known to have a wide range of health benefits,[163] would also be beneficial to mood. Indeed, a recent meta-analysis of eight RCTs found a positive effect of group-based gardening on depression.[164] Similarly, forest bating, which is pertinent to the Japanese traditional practice of Shirin-yoku, has been shown to have a positive effect on depression by a meta-analysis of four RCTs.[165] These activities provide opportunities to be exposed to not only green spaces but also other factors including sunlight and phytoncide.

Sleep

Sleep is a major determinant of resilience of modern-day humans. The modern age has made it possible to live a life that is not synchronized with the sun, which could result in a disruption of the sleep–wake rhythm of being active during the daytime and sleep during the environmental night with detrimental effects not only for sleep timing but also for our physical and mental health.[166] The amount of sleep required varies across individuals; however, approximately 7 to 8 h of sleep is generally considered standard and healthy for adults. A meta-analysis of seven longitudinal studies (totaling approximately 25,000 individuals) reported an increased risk of depression in both short and long sleepers compared with that in individuals with a standard sleep duration.[167] Not only insomnia of short sleep time but also alteration of the sleep–wake cycle and of the sleep structure are considered to be core symptoms of mood disorders.[168] Our research group's study using an actigraphy demonstrated that patients with major depressed episodes were lesser active during the day than healthy individuals but were rather more active and not sufficiently rested, such as being awake during the night.[169] Our subsequent study using a light wearable monitor attached to the chest, which monitored activity and heart rate variability simultaneously for consecutive 3 days, revealed that elevation in the sympathetic system during the sleeping time correlated with daytime inactivity in patients with depression.[170] Pertinently, we also found that psychiatric patients including those with bipolar depression and MDD showed increased rates of lower plasma orexin-A level in the morning,[171] which may reflect another pathological aspect of circadian rhythm leading to inactivity in daytime because orexin is an important regulator of wakefulness.[172] To reduce sympathetic activity during the night, it is advisable not to think about stressors and interpersonal conflicts before and throughout the bedtime since rumination on stressful events induces sympathetic arousal.[173]

The activity cycles of the body and brain are regulated by central and peripheral clocks. It has been emphasized that the unnatural input of light in modern times tends to disrupt functions of the body's clocks, especially the central clock, and causes them to stop cooperating with the clocks of the peripheral organs, and this may be one of the core pathologic factors in depression.[174,175] In fact, depressive disorder is almost always accompanied by sleep disturbances, and lack of sleep is an established risk factor for depression; in other words, depression and insomnia are bidirectionally related to each other.[176] Resetting the central clock located in the suprachiasmatic nucleus by exposure to sunlight in the morning and resetting the peripheral clock by eating breakfast would put the body and mind in an active mode,[177] which is crucial in the treatment of depressive disorder as well as in leading a vibrant life.[174,175]

Screen Time

At present, another factor that weakens resilience is called "screen addiction" such as addiction to video games and the internet. A data from the UK Biobank study ($N = 31{,}361$) revealed that there is a bidirectional association between higher discretionary screen time and poor sleep.[178] Epidemiological findings suggest that spending a lot of time looking at screens increases the risk of depression, which was demonstrated in a meta-analysis of studies examining the association between sedentary behavior (i.e. looking at screens such as computers and televisions) and risk of depression.[179] A meta-analysis of studies on children and adolescents also reported an association between screen time and risk of depression, with 1 h per day having the lowest risk and with the risk of depression increasing as the number of hours increases beyond 2 h.[180] In addition, a 2-year follow-up study of elementary school fourth- to sixth-grade students in Singapore reported that "pathological gamers" were more likely to have depression, anxiety, social anxiety, and lower grades.[181] Lockdown and restriction due to the COVID-19 pandemic have had further impact on screen time and sedentary lifestyle particularly in children and adolescents.[182] An intervention to reduce the use of screen electronic devices in the evening reported that the reduction of screen time after 9 PM correlated with earlier sleep onset time and increased total sleep duration, the latter of which led to improved daytime vigilance in adolescents.[183]

Molecular Mechanisms

There are at least four important biological systems/markers involved in the pathophysiology of depression: (i) the monoamine systems (the dopamine system, in particular); (ii) stress response by the hypothalamic–pituitary–adrenal (HPA) axis and autonomic nervous system; (iii) chronic

inflammation; and (iv) dysfunction of neurotrophic factor such as brain-derived neurotrophic factor (BDNF).[184–187]

As described above, there is a bidirectional association between excessive energy intake and depression, and a negative spiral association between the two can be a factor leading to intractability of both conditions. In obesity, metabolic syndrome, and diabetes, hypertrophy of the adipose tissue induces hypoxia and an inflammatory response such as an infiltration of macrophages. This changes the profile of the adipose tissue to being proinflammatory, leading to decreased anti-inflammatory adipokine, adiponectin, while increasing the secretion of proinflammatory adipokines, leptin and resistin, followed by increased proinflammatory cytokines such as IL-6 and TNF-α.[188] These peripherally increased proinflammatory cytokines can have access to the brain, which induces neuroinflammation and influences microstructure and functions of the brain that contribute to the development of depression.[189] In line, our research group demonstrated that the levels of the inflammatory cytokines IL-6, interferon β, and complement C5 were elevated in the CSF of patients with depression compared with that in healthy individuals.[190–192] The elevated IL-6 in CSF of patients with depression was confirmed by a subsequent meta-analysis.[193] Possible mechanisms of cytokine-induced depression include activation of the HPA axis (induction of extrahypothalamic corticotropin-releasing hormone and arginine vasopressin), development of glucocorticoid resistance, activation of indoleamine 2,3-dioxygenase leading to excitotoxicity, and increased expression of serotonin transporter.[194,195] Adherence to a healthy diet style such as the Mediterranean diet, a "less inflammation-prone diet," and adequate intake of Ω3 PUFA would result in less inflammatory conditions as described above. Exposure to food allergy should be avoided since it may induce inflammation.

In addition to inflammation, insulin resistance and leptin resistance are supposed to be involved in the pathophysiology of the bidirectional relationship between depression and excessive energy intake.[196] A molecular basis underlying the antidepressant actions of calorie restriction might involve orexin signaling activation and increased BDNF function.[35,197]

Nutritional imbalances are substantially relevant to the monoamine theory of depression. Iron is required as a cofactor in the

Table 1. Recommendable lifestyle modification interventions in the protection and treatment of depression (prepared by the author)

1. In cases of obesity, diabetes, and metabolic syndrome, provide nutritional guidance to promote appropriate energy intake (possibly calorie restriction/fasting).
2. In patients with depression and comorbid diabetes, antidiabetic drugs such as metformin and a glucagon-like peptide-1 agonist may be beneficial for both conditions.
3. If there is excessive energy intake, select an antidepressant that is less likely to cause weight gain.
4. Recommend healthier foods (e.g. vegetables, soy products, liver, fish, whole grains, and nuts) and avoid unhealthy food such as ultraprocessed foods.
5. Supplementation with Ω3 polyunsaturated fatty acids EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) for those who do not consume enough fish.
6. Promote adequate protein intake to ensure adequate amino acids.
7. Measure blood levels of vitamins, folic acid and vitamin D in particular, and provide supplementation for those who have any deficiency.
8. Exposure to sunlight should be recommended especially for individuals with an inadequate or deficient level of vitamin D.
9. For minerals, measure stored iron (ferritin) and zinc concentrations and provide supplementation for those who show insufficient levels of these minerals.
10. Promote adequate intake of dietary fiber, which is abundantly contained in whole grains, legumes, vegetables, and fruits.
11. Consider dietary supplements containing multivitamin and minerals for individuals with an unhealthy diet.
12. If appetite loss is significant, comprehensively check blood levels of vitamins and minerals and provide supplementation for those with deficient nutrients.
13. Recommend consumption of tea, green tea, and coffee (no sugar) over sugar-sweetened beverages but avoid consumption in the evening. Supplement of theanine would be of use.
14. Avoid alcohol consumption before bedtime in order to fall asleep.
15. Generally prohibit alcohol during treatment of depression.
16. Recommend foods with probiotics, such as yogurt, and actively use probiotics particularly in cases of irritable bowel syndrome and related abdominal symptoms.
17. Herbs such as St John's wort can be considered if taken in compliance with instruction or after consultation with a clinician.
18. Avoid exposure to food allergens.
19. Recommend nutritional guidance from a dietitian when there are nutritional problems.
20. Encourage oral hygiene.
21. Encourage cessation of smoking to smokers and use smoking cessation outpatient clinics, if appropriate.
22. Recommend exercise particularly aerobic and resistance training (in small steps gradually for patients with depression).
23. Enhance physical activity level in daily-life activities such as house chores, commuting, and shopping.
24. Ensure adequate sleep and a regular daily rhythm.
25. Get sun exposure and consume breakfast in the morning to regulate the central and peripheral clocks and get the body and mind prepared for vibrant activity.
26. Recommend light exercise or walking for 15–30 min in the morning, which has triple actions: physical activity, resetting the circadian clock, and increasing the vitamin D level.
27. Keep close connection to green (vegetation) and blue (surface water) spaces.
28. Gardening and forest bathing are recommendable recreational activities.
29. Avoid prolonged nonoccupational or nonacademic use of the internet and games and restrict screen time in the evening.
30. Avoid thinking about stressors and interpersonal conflicts before and during bedtime and relaxation should be recommended before bedtime.

production of monoamine neurotransmitters as shown in the Fig. 1 In line, iron deficiency does cause dopaminergic dysfunction as demonstrated by the RLS as mentioned above. In our CSF studies, reduced dopamine metabolite was found in patients with MDD.[96–98] The active metabolite of folate, 5-methyltetrahydrofolate is suggested to stabilize, enhance production of, or possibly act as a substitute for tetrahydrobiopterin, an essential cofactor in monoamine neurotransmitter biosynthesis.[198] Further, methionine and folate are involved in the methylation cycle donating one-carbon compounds such as methyl (CH_3-) and formyl (CHO−) groups for the production of DNA, proteins, phospholipids, and catecholamines. Thus, deficiency in folate and methionine could contribute to impaired monoamine production. Furthermore, it is known that when homocysteine accumulates due to some abnormality in the methylation cycle, hyperhomocysteinemia occurs, which increases the risk of heart disease and various neuropsychiatric disorders including depression.[199]

Zinc plays several functions relevant to the pathophysiology of depression in the brain as detailed below. In the brain, zinc is abundant in the glutamatergic system and exerts an agonistic action in the a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor and antagonistic action in the NMDA, metabotropic glutamate 1, and metabotropic glutamate 2 receptors.[200–202] Antagonistic action to NMDA receptors might serve against the excitotoxicity by the neuroinflammation described above. Zinc deficiency induces elevated activity of the HPA axis and glucocorticoid release.[203] Zinc deficiency also increases proinflammatory cytokines and causes detrimental effects in the brain as described.[204] Further, extracellular zinc binds to the dopamine transporter and suppresses reuptake of dopamine into neurons.[205] Moreover, zinc has antioxidant action and protects the brain against oxidative stress.[206] It also protects the barrier function of the blood-brain barrier (BBB).[207] Impaired barrier function has also been implicated in the pathogenesis of depression.[208,209]

Vitamin D is generated in the human brain and acts on diverse brain structures including the prefrontal cortex, hippocampus, cingulate gyrus, thalamus, hypothalamus, and substantia nigra. In neurons it suppresses oxidative stress, inhibits inflammation, provides neuroprotection, downregulates a variety of inflammatory mediators, and upregulates a wide variety of neurotrophins, including BDNF,[210] all of which are involved in the pathophysiology of depression.

Our research group demonstrated, for the first time, that CSF BDNF propeptide, a proxy marker for BDNF, is reduced in patients with MDD compared with healthy controls,[211] which is the direct evidence for the BDNF hypothesis[212] in live material. In studies using mice models, exercise has been reported to increase BDNF and neurogenesis in the hippocampus and improve performance in memory and learning.[213,214] Research results in humans have also been accumulated, suggesting that exercise increases hippocampal volume and suppresses its age-related decline, which leads to enhanced cognitive function and prevents cognitive decline, respectively.[215,216]

A decrease in so-called beneficial bacteria (dysbiosis) in the intestine results in decreased short-chain fatty acids such as butyrate, which induces increased intestinal permeability and inflammation of intestinal origin.[217] Intestinal inflammation induced by increased permeability and lipopolysaccharide or bacterial infection correlates with elevated microglial activation and release of proinflammatory cytokines in the brain.[218] Butyrate also plays a role in stimulating intestinal vagal nerves,[219] and dysbiosis of gut microbiota would cause a hypersympathetic state. Elevated activity of the HPA axis may also occur. In line, the probiotic *Lactobacillus johnsonii* was shown to induce activation of vagal sensory neurons innervating the gastrointestinal tract.[220] Further, short-chain fatty acids such as butyrate are known to enhance the integrity of BBB as well as the intestinal epithelial barrier by facilitating the assembly of tight junctions.[217] The increased BBB permeability allows proinflammatory cytokines and inflammation-inducing proteins such as fibrinogen to penetrate the BBB and enter into the brain, which leads to neural inflammation.

Conclusions and Recommendations

As detailed above, many lifestyle factors of diet, exercise, sleep, and related habits are associated with the risk of depression, and interventions addressing lifestyle factors have been found to be effective in the protection and treatment of the illness. Each healthy lifestyle habit reduces the risk of depression in multiple biological mechanisms. Based on the findings, the author summarizes 30 recommendable interventions in the prevention and treatment of the illness (Table 1). This points to the importance of lifestyle modification as well as psychotherapy and pharmacotherapy in the daily clinical setting. This could improve refractory patients who do not respond to conventional drug-based therapies.

Author contributions

This article was prepared and written by a single author.

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