Review

Key Nutrients for Optimal Blood Glucose Control and Mental Health in Individuals With Diabetes: A Review of the Evidence

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Review

Key Nutrients for Optimal Blood Glucose Control and Mental Health in Individuals With Diabetes: A Review of the Evidence.

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Abstract: Nutrition, diabetes, and mental disorders are interconnected and significantly impact an individual's overall health and well-being. This comprehensive review aims to explore the complex interplay between nutrition, diabetes, and mental disorders, highlighting the latest research findings in this field. While the influence of nutrition on the development and management of both diabetes and mental disorders is widely recognized, there remains a gap in understanding the intricate interplay between nutrition, mental health, and diabetes. Diabetes is associated with an increased risk of mental disorders, including depression, anxiety, and cognitive decline. Mental disorders can also contribute to the development of diabetes through various mechanisms including increased stress, poor self-care behaviors, and adverse effects on glucose metabolism. Thus, the mechanisms linking nutrition, diabetes, and mental disorders are complex and multifactorial. Inflammation, oxidative stress, gut microbiota alterations, and neuroendocrine dysregulation have emerged as potential pathways that may mediate the relationship between nutrition, diabetes, and mental disorders. Additionally, deficiencies in key nutrients such as omega-3 fatty acids, vitamin D, B vitamins, zinc, chromium, magnesium, and selenium have been implicated in the pathogenesis of both diabetes and mental disorders. Our findings indicate that use of personalized dietary interventions and targeted nutrient supplementation can improve metabolic and mental health outcomes in patients with type 2 diabetes.

Keywords: diabetes; mental health; anxiety; depression; supplementation; nutrients; blood glucose; nutrition; omega-3 fatty acids; vitamin D; vitamin E; vitamin B6; vitamin B12; folate; selenium; chromium; iron; magnesium

1. Introduction

The prevalence of diabetes has more than doubled in recent years, making it one of the most devastating diseases of the 21st century [1]. Approximately 415 million individuals with diabetes globally were reported by the International Diabetes Federation; this number is projected to increase to 640 million before the year 2040 [2]. The mortality rate of diabetes is alarmingly high. It has been reported that 1.5 to 5.1 million people per year lost their lives due to diabetes and related complications, placing it as the 8th leading cause of death worldwide [3]. According to the Diabetes Control and Complications Trial (DCCT), strict glycemic regulation decreases the risk of developing diabetes complications [4] and can significantly improve comorbid conditions, such as mental health disorders [5].

Depression and anxiety have often been linked to diabetes [6]. While some researchers have shown that diabetes is a risk factor for developing depression and anxiety [7], other studies have found that depression and stress are risk factors for type 2 diabetes [8,9]. Making changes to one's lifestyle, including diet, can significantly reduce the onset of many chronic health conditions and can also help alleviate symptoms if they are already present [10]. Depression and anxiety can negatively affect the quality of life of individuals due to the impact of symptoms and adverse effects [11]. Additionally, the biological, cognitive, and behavioral systems linked to mental disorders increase the risk of developing diabetes [8]. Constant stimulation of the hypothalamic-pituitary-adrenocortical

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(HPA) axis, in addition to hyperglycemia (biological), leads to diminished brain function (cognitive), which can foster poor nutrition as well [12]. Chronic stress can generate dysfunction directly or through the HPA axis, augmenting the production of inflammatory cytokines, which affect the functioning of pancreatic β-cells, creates insulin resistance, and ultimately can lead to diabetes [12]. Anxiety and depression have also been noted to negatively influence eating patterns and food choices [13]. This behavior may contribute to adiposity and the risk of developing diabetes [14]. Changes in appetite and lack of interest in physical activity (behavior) can further trigger the development of diabetes [15].

In addition, diabetes self-management, which typically entails perpetual management of blood glucose levels and sometimes taking insulin injections may increase emotional burden and mental disturbances [16,17], which can result in depressive and anxiety symptoms. Although the best quality of care among individuals with diabetes typically helps improve diabetes symptoms, other factors heighten the risk of developing depression and anxiety, such as worry about the increase in morbidity and mortality of the condition, developing related complications, and risk of hypoglycemia [18,19]. The incidence of depression has been noted to be high among people with diabetes compared to people with normal glycemic levels [20]. Depression impacts one in four adults with diabetes, while only 25% to 50% of these individuals are diagnosed and receive treatment [6]. One way to prevent or alleviate symptoms of such conditions is through a well-balanced diet and supplementation with essential nutrients. This literature review will assess how improved nutrition can prevent or treat mental disorders, diabetes, and related complications.

2. Materials and Methods

A comprehensive literature review was performed to investigate current evidence of the effects of different nutrients in preventing or treating mental health disorders and diabetes. Inclusion criteria included observational studies, randomized control trials (RCTs), systematic reviews, and meta-analyses published between 2008 and 2023. Databases were accessed and searches were performed through the George Mason University Library, PubMed, and Google Scholar. These keywords and phrases were used to increase the effectiveness of searches within the databases: “diabetes” or “depression” or “anxiety” or “mental health” or “risk factors” or “symptoms” or “mechanisms” or “nutrients" or “diet” or “nutrition”, or “ omega-3 fatty acids “or “vitamin B6” or “folate” or “B12” or “vitamin D” or “vitamin E” or “zinc” or “chromium” or “selenium” or “magnesium” or “iron”.

3. Results

Optimizing nutritional status is a key component of diabetes management, mental health, and general well-being [21]. Over the past two decades, the influence of diet on diabetes and brain health has been considered a modifiable risk factor for preventing related complications [22]. It has been shown that individuals with diabetes who follow a specialized diet can maintain the best glycemic control and decrease the chance of diabetes-related complications [23–30]. Over the years, studies have pointed to reducing or restricting carbohydrate intake, particularly simple carbohydrates, in preventing diabetes and reducing anxiety [31]. Carbohydrates are essential macronutrients for the body and brain [32]; however, a high intake of refined carbohydrates is associated with cognitive impairment, emotional stress, and negatively affects brain function and overall health [33]. Therefore, it is generally recommended that diet therapy should limit the quantity of refined carbohydrates and increase dietary fiber consumption [34].

Studies suggest that frequent intake of dietary fiber mitigates anxiety [35], slows the absorption of carbohydrates, and enhances insulin sensitivity, thus better-controlling blood glucose [36]. Dietary fiber also has the potential to change the gut microbiota [37]. It interacts with the gut microbiota to produce short-chain fatty acids (SCFA), which help improve glucagon-like peptide 1 (GLP-1) and blood glucose levels [38]. The positive outcome of SCFA on blood sugar regulation, body mass index (BMI), resting energy expenditure, and lipolysis has been shown in both animal [39] and human [40] studies. Indeed, gut microbiota has also been shown to play a critical role in mental health [41]. Microbiome studies have indicated that SCFA-producing probiotics such as Bifidobacterium, Lactobacillus, and Clostridium species have a positive effect on various psychiatric disorders, including anxiety [42]. Overall, the different study findings point to the need for limiting the intake

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of simple carbohydrates and a high intake of dietary fiber for comprehensive anxiety and diabetes care.

In addition, poor nutritional intake of essential nutrients can impact the body's ability to produce hormones and neurotransmitters and further influence blood glucose levels and mental health [43]. Polyunsaturated fatty acids, notably omega-3, vitamin D, vitamin E, B vitamins, zinc, magnesium, chromium, selenium, and iron are the most important nutrients for improving mental health, blood glucose, and diabetes-related complications [44,45]. Simple sugars, saturated fats, and sodium, on the other hand, can be hazardous to cerebral function and contribute to diabetes and related complications [46,47].

Polyunsaturated Fatty Acids

Omega-3 fatty acids have shown positive effects on mental health [48]. Additionally, long-chain omega-3 polyunsaturated fatty acids (PUFAs) eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3) have favorable relationships with risk factors for diabetes, mental health disorders, inflammation, and adiposity [49]. Although EPA and DHA have district functions, they perform best when combined. For instance, DHA is known to lower the production of pro-inflammatory cytokines in fat cells, causing the reduction of inflammation, while EPA is efficient in lowering triglycerides and thereby decreasing inflammation [50,51]. In a meta-analysis, omega-3 supplements have been shown to improve fasting blood glucose and reduce insulin resistance [52]. Thus, increasing intake of omega-3 fatty acids as bioactive anti-inflammatory agents is recommended to reduce prediabetes's progression to full-blown type 2 diabetes [53,54]. The positive effects of omega-3 on mental conditions such as anxiety, depression, and the mental consequences of sleep disturbance have also been reported [55]. The key evidence for the effectiveness of the two main omega-3 fatty acids in fish oil, EPA and DHA, have been obtained in the treatment of depression and anxiety symptoms [56]. It has been shown that a daily dosage of 1.5-2 g of EPA improved depressive symptoms and enhanced mood [57].

Mental health disorders have been linked to irregularities in fatty acid structure [58]. Lower omega-3 fatty acid concentrations are correlated with cerebral disorders [58]. In a recent report, DHA was noted to possess a higher propensity to accumulate cholesterol-rich lipid rafts compared to EPA, in addition to having a superior potential to impact neural signaling, ultimately impacting mental health [59]. Previous reports have detected an association between depression and low consumption of omega-3 fatty acids, while other studies show reduced levels of omega-3 fatty acids in red blood cell membranes in patients suffering from depression and anxiety [60]. Omega 3's are not only essential for reducing or preventing symptoms of anxiety and depression but also have beneficial effects on lowering cardiovascular disease risk, major causes of mortality in patients with and without diabetes [61,62]. The evidence for the protective nature of omega-3 fatty acids on the heart is abundant; present guidelines suggest that patients with cardiovascular disease should consume at least 1 g of omega-3 fatty acids from either fish or fish oil supplements daily, whereas individuals without CVD are recommended to consume at least 250–500 mg daily [63].

Vitamin B

Vitamin B complex, including B6, B12, and folate, has numerous benefits to brain health and psychological well-being [64,65]. These water-soluble vitamins are vital for optimum brain functioning and the creation of neurotransmitters [66] while neurological disorders, including anxiety and depression, have been reported in cases of deficiency of these micronutrients [67]. It has recently been discovered that taking high doses of vitamin B6 supplements significantly reduces anxiety, stress, and depression: supplementing adults with 25mg of vitamin B6 twice daily for six months improved symptoms of anxiety and depression [68]. Another, even more recent study reiterates the significance of vitamin B6 and supports the use of such supplements to enhance cognitive function and improve mental well-being [69]. In a longitudinal community study, individuals who had a higher dietary intake of vitamin B6 ($\geqslant$1.71 mg/day for women) and B12 ($\geqslant$4.79 μg/day for men) had a lower incidence of depression [70]. It has also been reported that folate and B12 deficiency can cause neurological complications, such as anxiety and depression [71]. During pregnancy, it has been found that a high level of folate, coupled with low levels of B12 is associated with gestational diabetes [72]. Conversely, B6 effectively lowers blood glucose levels among patients

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with gestational diabetes [73]. In addition, a study conducted by Kim et al. revealed that vitamin B6 has the potential to lower postprandial blood glucose levels after consuming sucrose and starch [74]. This effect is attributed to the inhibition of small-intestinal α-glucosidase enzyme activity. Additionally, vitamin B complex has demonstrated enhancement of glycemic control and renal function in patients with diabetes by reducing homocysteine levels [75].

Vitamin D

Vitamin D is as crucial to diabetes control and mental well-being as it is for bone health [76,77]. Studies have shown that vitamin D deficiency negatively impacts insulin sensitivity [78]. There is evidence that vitamin D can directly increase insulin secretions from pancreatic β-cells [79]. Additionally, supplementing with vitamin D significantly improved fasting blood glucose, insulin, and HOMA-IR in patients with diabetes [80]. Diabetes development is characterized by the ineffectiveness of insulin, modifications in pancreatic β-cells, and higher levels of inflammation [78]. There is a link between these conditions and vitamin D deficiency [78]. This fat-soluble vitamin alleviates not only depressive and anxiety symptoms but also improves immune function [81–83]. Studies have identified inflammation and oxidative stress as part of the pathophysiology of type 2 diabetes and mood dysfunction [84–86]. A deficiency of vitamin D among people with diabetes is linked to depression and anxiety [82]. Thus, screening for vitamin D levels is useful in both conditions. When systemic inflammation occurs due to diabetes, modified functions of β-cells including the putative stress signal to periphery can occur due to elevated cytokines, which further stimulate insulin resistance [87]. Vitamin D lowers systematic inflammation by reducing the generation of cytokines via hindering nuclear transcription [88,89]. In other words, it has been shown that optimal levels of vitamin D cause most intracellular oxidative stress-related events to be downregulated [90]. An individual's intracellular Nrf2 status is associated with the buildup of mitochondrial reactive oxygen species (ROS) and increase in oxidative stress [91,92]. In effect, Nrf2 safeguards cells from oxidative stress, which is controlled by vitamin D [93,94].

Vitamin E

The significance of vitamin E in the prevention and maintenance of diabetes and co-existing complications cannot be overemphasized. An increase in glucose in the blood increases oxidative stress, which promotes the onset and progression of diabetes and co-occurring symptoms [95]. Vitamin E is a lipid-soluble antioxidant found in cell tissues that act as a shield against lipid peroxide, hence is required for the regular functioning of immune cells [96]. Vitamin E plays a pivotal role in glucose homeostasis and can prevent the onset of diabetes and control and prevent diabetes complications [97]. In a trial of healthy adults, it was found that a high dose of vitamin E supplementation (300 mg/d) reduced lipid peroxidation [98], while another study showed that the simultaneous administration of Vitamins E and C resulted in reduced inflammation and enhanced insulin action by promoting non-oxidative glucose metabolism [99]. These findings support the role of vitamin E in the prevention of type 2 diabetes and related complications. In several studies, when vitamin E was co-administered with atorvastatin and vitamin C in people with type 2 diabetes, blood glucose levels decreased [100,101].

The human brain is vulnerable to antioxidant deficiency, which can result in oxidative damage [102]. Deficiency of vitamin E is linked to both depression and anxiety [103] while an association between increased intake of vitamin E (up to 15 mg/day) and a reduction in depressive symptoms has been observed [104]. Evidence indicates that ideal concentrations of vitamin E depend on PUFA consumption, such as dietary linoleic acid [105]. Thus, individuals with insufficient vitamin E are often predisposed to psychological problems that are linked to the protective effect of vitamin E against harm to PUFA in cell membranes [106,107]. Optimal vitamin E requirements remain uncertain, as requirements depend on the concentrations of PUFA in the diet [108]. Thus, increased intake of PUFA, coupled with low consumption of vitamin E, leads to vitamin E deficiency, which increases the risk of depressive and anxiety conditions [105]. The recommended level of vitamin E intake should thus be based on the individuals' risk for diabetes and mental health conditions.

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Zinc

Zinc is a critical micronutrient involved in several cell functions and necessary for glycemic regulation [109]. While some studies have reported lower levels of zinc among people with diabetes [110], other reports have also emphasized that zinc deficiency is often associated with reduced responsiveness to insulin [109]. In a recent meta-analysis (n = 3978 subjects), supplementation with zinc improved fasting glucose concentrations [111]. Zinc is an important cofactor in glucose homeostasis, supports the function of the immune system, and reduces oxidative stress [112]. Several complications of diabetes are linked to free radicals and raised intracellular oxidants which are caused by decreased intracellular zinc and other antioxidants [113]. In essence, supplementation with zinc can guard against oxidative damage at the onset of diabetes [114] and have favorable antioxidant effects, which decrease the risk of patients developing diabetes-related complications [115].

Depression and anxiety are also associated with low intake of dietary zinc [116]. Zinc-containing neurons form a trail through the cerebral cortex, hippocampus, and amygdala, impacting mood and cognitive ability [117]. Zinc deficiency was found to be common among patients with depression and anxiety [118]. In summary, zinc is beneficial in both the prevention and management of diabetes, as well as the mental well-being of patients with diabetes.

Magnesium

Magnesium is a cofactor for more than 300 enzymes involved in cholesterol synthesis and glucose metabolism [119]. The association between diabetes and hypomagnesemia in extracellular and intracellular compartments is well-established [120]. Magnesium deficiency has been linked to insulin resistance, leading to hyperglycemia [121,122]. Plasma magnesium concentrations have an inverse relationship with insulin resistance, and supplementation with magnesium enhances insulin sensitivity in people with diabetes [123]. A previous study suggested that hypomagnesemia among people with diabetes may be due to excessive urinary excretion [124]; thus, adequate dietary intake of magnesium or supplementation is recommended to maintain optimal levels [125].

Psychological disorders such as depression and anxiety also occur in individuals who have magnesium deficiency. In a randomly selected, population-based study, the relationship between magnesium and mental disorders was observed using a validated food frequency questionnaire and the General Health Questionnaire-12 to assess psychological symptoms [126]. Although there was no association between anxiety and magnesium levels, a link between a deficit of magnesium and depression was detected. Additionally, other studies noted quicker recovery from psychiatric disorders after patients' magnesium levels improved [127], and that 125–300 mg of magnesium taken with meals at bedtime had improved severe depression symptoms within a week [127]. Neuronal magnesium deficiency occurs when stress hormones are induced, and calcium levels are extremely high [128]. A randomized, control trial found that supplementing with magnesium aided in treating depression among people with diabetes, with no reported adverse effects [128].

Chromium

Chromium, an essential mineral, is important in lipid and carbohydrate metabolism and aids in improving glycemic control, and can prevent the onset of diabetes and related complications [129]. Recent studies have revealed that low levels of chromium have been associated with an increased risk of diabetes, while optimum levels of chromium enhance glucose homeostasis in patients with hyperglycemia [130]. Further, deficiency of chromium has been linked to elevated inflammation and increased cardiometabolic risk [131]. Several RCTs have also found significant improvements in diabetes complications after serum levels of chromium were improved in the treatment groups [132–134]. Given the evidence, it is best to maintain optimum levels of this mineral by consuming chromium-rich foods. Good dietary sources of chromium are whole-grain foods, egg yolks, green beans, broccoli, and meats [135].

Mental health disorders have also been associated with low concentrations of chromium [136]. In a recent study, subjects aged 18-40 years randomized to receive 200 μg/d chromium experienced improvements in their anxiety and depressive conditions [137]. In a similar double-blinded study, it was found that supplementation with 400 μg/d of chromium for two weeks, followed by 600 μg/d for four weeks reduced carbohydrate cravings among individuals with depression symptoms, while reducing mood swings [138,139].

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Selenium

The benefits of dietary selenium in reducing the risk of diabetes are currently inconclusive [140]. While some studies have shown a positive effect in preventing the onset of diabetes [141], others have shown the opposite effect [142]. The RDA for selenium is 55 μg/d for both men and women [143]. Although some researchers claim that optimum blood concentrations of selenium are required to reduce the risk of type 2 diabetes, large cross-sectional and intervention trials confirm, rather, that supplementation among people who already have an adequate intake of selenium might increase their risk of type-2 diabetes [140,141,144]. Collectively, selenium appears to possess both beneficial and toxic effects. The preventive effect of selenium is attributed to the antioxidant role of selenoproteins and selenocysteine [145]. Conversely, excessive intake of this essential trace mineral causes selenium compounds to produce oxygen species. In the event of oxidative stress, oxygen radicals may enhance insulin resistance and alter the function of the pancreatic β-cells [146]. The relationship between high levels of selenium and hyperglycemia is indeed complex, as individuals with high selenium levels have enhanced superoxide anion production [147–149]. Hydrogen peroxide which is produced in the body condenses to water by glutathione peroxidase; however, concerns have been raised over the lower activity of antioxidant enzymes such as glutathione peroxidase and superoxide dismutase in diabetes [150]. There is also evidence that selenium deficiency not only impacts glucose control negatively [151] but is also linked to a heightened risk of cognitive decline, depression, and anxiety [144,152,153]. Therefore, it is best to have an adequate intake of this essential mineral from dietary sources.

Iron

Low serum iron concentration is the most common nutrient deficiency globally and increases the risk of various health conditions, including mental health disorders [154]. The incidence of anemia among individuals with a mental disorder is significantly greater than in the general population [155]. Iron is a crucial component of neurotransmitters and DNA synthesis [156,157]. It has been shown that a low serum concentration of iron is associated with depression and anxiety [158]. In a recent study, it was established that a lack of iron-stimulated modifications in the hippocampus and corpus striatum, increases the risk of developing anxiety and depression [159]. Iron is a vital component of hemoglobin, as well as several enzymes in cellular metabolism that are critical for improving the central neurological structure [160]. A meta-analysis of data demonstrated a link between iron supplementation and significant enhancements in task performance, memory, and ultimately an improvement in mood and reduction of depressive symptoms [161].

In contrast, increased iron intake enhances the risk of diabetes and its complications [162]. Iron overload affects vital tissues by quickening mitochondrial decay and causing systemic free radical destruction of healthy tissues [163,164]. Excessive iron accumulation can impact critical tissues involved in glucose and lipid metabolism, such as pancreatic β cells, liver, muscle, and adipose tissue, as well as organs affected by chronic complications of diabetes [165]. Excessive iron intake has consistently been found to increase ferritin, insulin resistance, and glycosylated hemoglobin, and may also increase diabetes complications [166]. One of the distinctive functions of iron is its ability to be changeably oxidized and reduced, yet creates a pro-oxidant molecule to produce strong reactive oxygen species [157]. In a randomized control trial, iron depletion in patients with diabetes who had high serum ferritin levels (>200ng/ml) improved vascular dysfunction [167]. Fundamentally, maintaining iron homeostasis is critical, and an overload of iron could be a risk factor for diabetes.

4. Discussion

Proper nutrition plays a vital role in both preventing and managing blood glucose levels as well as promoting mental well-being in individuals with diabetes. Several micronutrients have been implicated in blood glucose control and mental health in patients with diabetes. Vitamin D, for example, has been shown to play a role in insulin secretion and sensitivity, and low levels of vitamin D have been associated with an increased risk of diabetes and mental health disorders, including depression and cognitive decline. B vitamins including B6, B9, and B12 are also involved in glucose metabolism and nerve function, and deficiencies in these vitamins have been linked to impaired glucose control and mental health disturbances. Furthermore, minerals such as magnesium and

chromium have been shown to affect insulin sensitivity and glucose metabolism, and adequate intake of these minerals may have beneficial effects on blood glucose control and mental health.

The mechanisms through which these key nutrients exert their effects on blood glucose control and mental health are complex and multifactorial. They may involve the regulation of insulin signaling pathways, modulation of inflammation and oxidative stress, and influence on neurotransmitter synthesis and function, among other mechanisms. Additionally, it is critical to pay attention to the recommended amount of these nutrients. For example, for nutrients such as vitamins B6 and B12, when administered in higher doses to research subjects with insufficient levels of the vitamins, there were significant improvements in their serum concentration levels while their symptoms also improved. On the other hand, higher doses of chromium, vitamin E, and folate, if dispensed to individuals in doses higher than RDA, might be toxic, increasing the risk of diabetes complications and mental health disorders.

Overall, adequate intake of the reported essential nutrients from the best food sources is a priority, as it has the potential to aid in glucose homeostasis, prevention or treatment of diabetes and related complications as well as mental disorders such as depression and anxiety. In cases where patients are unable to obtain sufficient nutrients through their diet, it is advisable to consider supplementation with the specific nutrients highlighted as a means to prevent and/or ameliorate diabetes and mental health disorders.

5. Conclusions

The evidence suggests that key micronutrients may help to concurrently optimize blood glucose control and support mental well-being. However, further research is needed to establish optimal nutrient recommendations for blood glucose control and mental health in patients with diabetes. Proper nutrition, in conjunction with appropriate medical care, can be a vital component of a comprehensive approach to both managing blood glucose levels and supporting mental health.

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