Role of Folic acid in Type 2 diabetes

ABSTRACT

The metabolic condition known as diabetes mellitus is marked by hyperglycemia, a host of symptoms affecting the heart, kidneys, nerves, and other organs. Diabetes nephropathy is one of the leading causes of diabetic impermanence and morbid state. Low parameters of pteroylglutamic acid in the blood are associated with Diabetic Nephropathy, whereas endothelial dysfunction increases the risk for T2D.

Endothelial dysfunction is associated with diabetes, which perhaps is caused by the disjunction of the endothelial nitric oxide (NO) synthase enzyme, which reduces NO availability. Because folic acid can repair the disjunction of NO synthase, we sought to see if pteroylglutamic acid supplementation may affect the function of the endothelial layer and inflammatory indicators in type 2 diabetes patients who did not have vascular disease.

Recent studies have shown that pteroylglutamic acid also has direct benefits on the function of endo, in addition to its natural function of lowering homocysteine. Folic acid might serve as a "biomarker" for the function of endothelial cells. Many mechanisms have been linked to higher total homocysteine levels and type 2 diabetes risk in diabetic patients. Higher folic acid levels altered endothelial-dependent vasodilation in T2D patients. In patients with coronary heart disease (CAD), folic acid supplementation has been found to reduce homocysteine parameters and improve the function of the endothelial layer. On the other hand, RCTs looking at IR and T2D outcomes have shown mixed results.

Several mechanisms link higher total homocysteine levels to increased risk of insulin resistance (IR) and type 2 diabetes mellitus(T2D). Treatment with folate has been shown to bring down homocysteine parameters and improve the endothelium functions in people with coronary heart

disease (CAD). Randomized controlled trials (RCTs) on IR and T2D outcomes, on the other hand, have produced a wide range of results.

INTRODUCTION

GDM is a severe national and global health concern defined as variable degrees of glucose intolerance that first appear during pregnancy. (1) Around 17% of the world's population is affected by GDM. GDM is relatively widespread in Southeast Asia, with 25.0 percent of people suffering from it. GDM increases the risk of poor pregnancy and neonatal outcomes and long-term metabolic disorders in both the mother and the child. (2)

With the prevalence of GDM increasing, it's more crucial than ever to have a more profound knowledge of the illness's risk factors and processes and develop appropriate treatments to assist women, and their children manage. (3) Pteroylglutamic acid serves as a source of single carbon units in the methionine/Hcy cycle by supplying 5-methyltetrahydrofolate for the methylation of Hcy back into methionine. S-adenosylmethionine is formed as a result of the methionine cycle (SAM). (4)SAM-dependent methylation activities are required for the synthesis of phosphatidylcholine (PC), an essential component of the plasma membrane, and very-low-density lipoprotein (VLDL).

As a result, lipid metabolism, Folic acid FA metabolism, and PC metabolism are all intertwined. Lower levels of methylenetetrahydrofolate reductase protein and activity have recently been linked to increased fat accumulation in mice (MTHFR). (5) According to another animal study, GDM is a severe national and worldwide health hazard described as varying degrees of glucose intolerance that first manifests during pregnancy. (6) GDM affects around 17% of the globe's citizenry. GDM has been quite frequent in Southeast Asia, affecting up to 25.0 percent of the population. (7) GDM raises the chance of poor pregnancy and neonatal outcomes, as well as the risk of both the mother and the child developing long-term metabolic problems. (8) Overeating fat causes lipid buildup. Excessive FA supplementation may thus lead to hyperlipidemia. Hyperlipidemia is well recognized as a significant risk factor for the growth of GDM. Although, a few studies have happened on the effects of dietary fat on plasma lipids in pregnant women.

Furthermore, no evidence taking an FA supplement increases your chance of developing GDM.(9)

The ability of FA to prevent neural tube malformations is widely documented (NTDs). FA supplementation guidelines have been widely accepted before and throughout pregnancy worldwide. According to the WHO, reproductive women should take 400g/d FA supplements for 4-12 weeks before pregnancy and 8-12 weeks throughout early pregnancy. (10) In reality, most women continue to take FA for more extended periods than the guidelines suggest. According to a recent Chinese poll, 48.8% of pregnant women used FA for more than 12 weeks before conception, and 30.7 percent used it for 12-24 weeks throughout their pregnancy.

Furthermore, according to an Irish study, 56.2 percent of women took FA for more than 12 weeks and 17.7% for more than a year before becoming pregnant. (11) The bulk of published research, to our knowledge, has focused on high FA doses or varying periods of FA usage, but no studies have explicitly looked into the effects of FA supplementation duration on pregnant women. As a result, it's unknown if long-term FA supplementation has any negative consequences, such as lipid metabolism or diabetes mellitus. Therefore, the basis of this analysis was to determine whether there was an interrelation linking the length of FA supplementation and the risk of developing GDM.

Researchers looked at the relationship between supplementation duration and blood lipid profiles to see if lipid profiles show a specific involvement in the interrelation linking pteroylglutamic acid supplementation with GDM. Long-we hypothesized that long-term FA supplementation raises blood lipid profiles, increasing the risk of GDM. (12)As a result, this research might give fresh insight into the long-term adverse effects of FA supplementation on GDM in Chinese women. Metformin works by lowering hepatic glucose synthesis and improving glucose excretion, which is suggested for people with T2D. Type 2 diabetes results from insufficient beta-cell requital for insulin resistance (IR) or tolerance to IR. It is one of the most commonly prescribed pharmacologic treatments for T2D all over the globe. Although, due to malabsorption lowers pteroylglutamic acid and cyanocobalamin levels while raising homocysteine levels (Hcy). Metformin affects folate, B12, and Hcy levels, but they are affected by the amount and duration

of metformin used. When methionine, an essential amino acid, is demethylated, it produces homocysteine, a sulfur-containing aminoalkanoic acid.

Irregularities of the endothelium, IR, prothrombotic condition, macroangiopathy, diabetic nephropathy, dyslipidemia, oxidative anxiety, and substandard disorder management have all been associated with high Hcy levels in people with diabetes. (13) The association of insulin resistance and plasma homocysteine parameters has been a source of contention. In two crucial epidemiological studies, hyperhomocysteinemia has been marginally but significantly connected to insulin levels and insulin resistance. In individuals with impaired fasting glucose, fasting serum homocysteine was significantly higher.

In T2D, they have been linked to an escalated chance of cardiovascular disorders and mortality. Elevated total homocysteine parameters have been associated with microalbuminuria, cognitive impairment, diabetic neuropathy, as well as foot ulcers. (14) As a result, in type 2 diabetes patients, reducing disseminating total homocysteine parameters may assist in minimizing cardiovascular cases, as well as morbidity and mortality.

In one of two remethylation processes, Hcy can remethylate to methionine or trans-sulphurate to cysteine, with pteroylglutamic acid serving as a methyl contributor in both. Furthermore, vasculogenicotoxic effect is thought to be mediated by several routes, most of which are associated with the loss of endothelium-regulating functions. (15) Endothelial cell injury, reduced nitric oxide accessibility, oxidative anxiety, smooth muscle cell division, improved leukocyte adhesion, rapid platelet aggregation, impaired fibrinolysis, and the establishment of a chronic inflammatory condition have all been linked to homocysteine-induced vascular disease.

Due to an affirmative relationship linking bodyweight with Hcy concentration and an approving knowledge on the effect of folic acid on parameters of glycemic control, insulin resistance, total cholesterol, TG, LDL-C, HDL-C, serum folic acid and cyanocobalamin, plasma homocysteine, the RCT was conducted to evaluate the impacts of oral pteroylglutamic acid supplementation for eight weeks on parameters of fasting blood glucose, glycated hemoglobin(hemoglobin A1c), serum insulin, IR as well as total cholesterol.

Methodology

The keywords "folic acid," "homocysteine," "endothelium," "type 2 diabetes," and "diabetes mellitus" were systematically searched in PubMed, Medline, Scopus, and Embase databases using the Medical Subject Headings(MeSH) terms, with slight changes depending on the sources for a search technique that is not limited to a single language. The reference lists of the articles we looked at were also used to acquire citations. Even though many items were evaluated but not mentioned in the text, the value of each piece dictated whether or not it was included.(16) The search usually yielded a large number of articles in the search box; items were then chosen based on originality and overall paper worth. Articles authored in languages other than English were translated into English using library resources and the internet.

Type 2 Diabetes

Type 2 diabetes (T2D), often known as adult-onset diabetes, is a type of diabetes marked by high blood sugar, insulin resistance, as well as insulin deficiency. Increased thirst, frequent urination, along with undetermined weight loss are all usual symptoms. Increased appetite, exhaustion, along with unhealed wounds are also viable symptoms. Symptoms manifest itself moderately - heart disease, strokes, diabetic retinopathy, which can lead to blindness, renal failure, along with poor blood flow in the limbs. All of which can lead to amputations and are long-term effects of high blood sugar. Ketoacidosis is rare, however abrupt start of hyperosmolar hyperglycemic condition is possible.

Obesity together with a lack of exercise are the leading causes of type 2 diabetes. Some persons are genetically predisposed to disease more than others.

Type 2 diabetes accounts for around 90% of diabetes cases, with type 1 diabetes and gestational diabetes accounting for the remaining 10%. Because of an autoimmune-induced loss of insulin-producing beta cells in the pancreas, type 1 diabetes requires a lower overall dose of insulin to

manage blood glucose. Blood tests, such as fasting plasma glucose, oral glucose tolerance test, or glycated haemoglobin, are used to diagnose diabetes (A1C).

Vitamin B9, Folate or Folic Acid

The term folate refers to 150 pteroilglutamate amino acids that are important cofactors in amino acid transamination, particularly homocysteine to methionine, and play a role in cell proliferation through enzymatic action in DNA purine base construction. A deficiency of folate has been associated with megaloblastic anaemia, neural tube abnormalities, cardiovascular disease, carcinoma, along with senile mental deterioration. Folates are found in animal tissue, leafy vegetables, legumes, as well as nuts.

The aetiology of T2D is linked to cyanocobalamin insufficiency along with hyperhomocysteinemia., and diabetics have been given supplements despite the fact that deficiency is uncommon. According to a case-control research, low folate and B-12 intakes were associated to hyperhomocysteinemia in type 2 diabetes patients.(17) By repairing DNA damage indicated by micronuclei, folic acid intake can help diabetics decrease the effects of oxidative stress. Folate supplementation has been shown to aid persons with type 2 diabetes improve their glycemia control by reducing glycated hemoglobin (hemoglobin A1c), fasting blood glucose, serum insulin, IR, as well as homocysteinemia. Pyridoxine, folic acid, and cyanocobalamin supplementation also has been demonstrated to alleviate diabetic retinopathy symptoms.

Because it is more stable during processing and storage, manufactured folic acid, which is turned into folate by the body, is used as a dietary supplement and in food fortification. Folate is needed for the body to create DNA and RNA, as well as to metabolise amino acids for cell division. Because humans cannot produce folate, it must be obtained through food, making it an important vitamin. It may be found in a variety of foods. In the United States, 400 micrograms of folate per day from meals or dietary supplements is suggested for adults.

Folate (as pteroylglutamic acid) is used to cure anaemia brought by a lack of folic acid. Women take pteroylglutamic acid supplements when going through the act of pregnancy to lower the

chance of neural tube defects (NTAs) in their babies. Low parameters in before time parturiency are thought to be the source of NTA's in more than half of all kids born. To reduce the occurrence of NTDs, more than 80 nations utilise either mandated or voluntary folic acid fortification of particular foods.Long-term folic acid intake has been linked to a slight lowering in the risk of MI as well as an increase in the risk of prostate carcinoma. Large doses of supplementary folic acid have raised concerns that they may mask vitamin B12 insufficiency.

Folate deficiency can occur if you don't get enough of it. This can cause anaemia, in which the red blood cells grow excessively big. Tiredness, cardiovascular issues, difficulty in breathing, open sores on the tongue, and modifications in skin or hair colour are all possible symptoms. Folate insufficiency in children can occur in as little as a month if their diet is inadequate. Total body folate levels in adults should be ranging from 10 and 30 mg, with plasma parameters more than 7 nmol/L (3 ng/mL). In the middle of 1931 and 1943, the mineral folate was found. It is listed as an essential medicine by the World Health Organization. With around 8 million prescriptions were published in 2019, it became the 89th most widely advised drug in the United States of America. As it had been discovered in shady-green leafy plants, the term "folic" was coined taking its origin from latin context folium (meaning leaf).

Although commonly used interchangeably, the terms "vitamin B9" as well as "pteroylglutamic acid" have slightly distinct meanings in various circumstances. The adjoining base of pteroylglutamic acid is referred to as folate in organic chemistry. Folic acids are a group of physiologically active chemicals related to and including pteroylglutamic acid that are studied in the field of biochemistry. The word "pteroylglutamic acid" is restrained as the produced version that is utilized as a dietary reserve, whereas "folic acid" is a group of vital nutrients linked to folic acid originating from plants.

Folate deficiency in pregnant women has been linked to neural tube abnormalities (NTAs), with an estimated 300,000 instances globally prior to the adoption of obligatory dietary fortification in many countries.] Because NTAs arise early in parturiency (in the 1st month), women must have plenty of folate before they conceive, which is why it is suggested that every woman hoping to get pregnant take a folic acid-containing dietary supplement before and during her pregnancy.

Many women fall pregnant without intending to, or may not discover they are pregnant until far into the first trimester, which is the important period for minimising the risk of NTAs. Countries have either mandated or voluntary dietary fortification of wheat flour and other grains, or have none at all as well as rely on public health and healthcare practitioner guidance to women of reproductive age. When mandated fortification was compared to nations with voluntary fortification or no fortification programme, there was a 30% reduction in live births with spina bifida, according to a meta-analysis of global birth prevalence of spina bifida.

Metformin, like vitamin B12, can induce folate insufficiency; a double-blind, randomized clinical trials found that diabetic males who took metformin plus folic acid tablets for eight weeks had improvements in homocysteine levels, total anti-oxidant volume, and malondialdehyde.

DISCUSSION

Males with T2D who were on metformin, short-term pteroylglutamic acid (5 mg daily) supplementation resulted in significant increases in blood folic acid, B12, and TAC, as well as reduces in plasma homocysteine and serum malondialdehyde.(18) Homocysteine, a sulfur-containing amino alkanoic acid, is generated when the essential amino alkanoic acid methionine.(19) Total Hcy levels have been associated with age, gender, smoking, intoxicating drinks use, malignancy, thyroid ailment, renal dysfunction, diet (folic acid, vitamin B6, and B12 deficiency), medicine, together with the methylenetetrahydrofolate reductase genotype. As a result, differences in Hcy might be linked to various factors.(20)

At dosages as low as 0.5 mg/d, pteroylglutamic acid supplementation has been evident to reduce plasma homocysteine parameters; the parameters ranged from 0.5 to 10 mg/d in other experiments. (21)When the levels of folate and Hcy are both within normal limits, folate supplementation reduces Hcy.FAS might help persons with type 2 diabetes reduce cardiovascular events, especially as a primary preventative treatment. (22-29)

Conclusions

Even though vitamins have a substantial impact on diabetes mellitus risk, development, and consequences, there is insufficient evidence to recommend independent or combination of many different vitamin supplementation in the diabetic population in most patients. Consuming a range of meals rich in vitamins in appropriate amounts is the most excellent strategy to achieve healthy nutritional status. Dietary evaluations are crucial to discover specific consumption deficiencies and offer suggestions. Overdosing or toxicity are risks associated with supplement usage, particularly regarding specific vitamins; these negative consequences are described. Pteroylglutamic acid plasma parameters determine endothelium-mediated vasodilation in type 2 diabetic cases. These findings back up the notion that pteroylglutamic acid directly influences function of the endothelial layer, as well as therapy aiming at raising pteroylglutamic acid levels to lower cardiovascular risk. Pteroylglutamic acid therapy decreased Hcy levels in the blood, improved glycemic control, and reduced IR in T2D cases. In T2D cases, using high dosages of metformin, pteroylglutamic acid supplementation decreases plasma homocysteine levels and improved glycemic control, insulin resistance, and folic acid together with cyanocobalamin levels. This discovery creates a safe and secure environment.

Ethical Approval:

As per international standard or university standard ethical approval has been collected and preserved by the authors.

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