

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 main causes of diabetic impermanence and morbid state. Low level of pteroylglutamic acid in the blood is associated with diabetic nephropathy, whereas endothelial dysfunction increases the risk for type 2 diabetes (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 has the ability to repair the disjunction of NO synthase, we sought to see if pteroylglutamic acid supplementation may affect function of the endothelial layer and inflammatory indicators in type 2 diabetes patients who did not have vascular disease.

Comment [S1]: Experimental study or a review??

Recent studies have shown that pteroylglutamic acid also has direct benefits on function of endothelial cells, in addition to its natural function of lowering homocysteine level. Folic acid might therefore serve as a "biomarker" for the assessment of function of the endothelial cells. A variety of 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 levels as well as improve function of the endothelial layer. Randomized control trials (RCTs) looking at insulin resistance (IR) and T2D outcomes, on the other hand, have shown mixed results.

Through several mechanisms, higher total homocysteine levels are have been linked to increased IR as well as the risk of the development of type 2 diabetes mellitus (T2D). Treatments with

folate have been shown to **reduced the levels of** homocysteine and improve functions of endothelium in people with coronary heart disease (CAD). RCTs on IR and T2D outcomes, on the other hand, have produced a wide range of **results**.

Comment [S2]: Repeated sentence; Abstract more than 300 words??

INTRODUCTION

Gestational diabetes mellitus (GDM) is a severe national and global health concern that is defined as variable degrees of glucose intolerance that first appears during pregnancy **among women population**. (1) Around 17% of the world's population is affected by GDM. **GDM is highly prevalent in Southeast Asia, with up to 25.0 percent of women affected by the condition**. GDM increases the risk of a poor pregnancy and neonatal outcome, as well as the risk of long-term metabolic disorders in both the mother and the child.(2)

With the prevalence of GDM increasing, it's **now** more crucial than ever to have a deeper knowledge of **the disease, its risk factors and complications**, as well as the development of appropriate treatments to assist women and their children manage **the condition**.(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 (**SAM**) is formed as a result of the methionine cycle. (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).

During lipid metabolism, folic acid (**FA**) metabolism, and PC metabolism are all intertwined. Lower levels of methylenetetrahydrofolate reductase **enzyme** and **its** activity have recently been linked to increased fat accumulation in mice (MTHFR).(5) According to another animal study, GDM is a serious 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 predisposes women** to poor pregnancy and neonatal outcome, as well as the risk of both the mother and the child developing long-term metabolic problems. (8) Eating too much fat cause's lipid buildup. Excessive FA supplementation may thus lead to hyperlipidemia.

Comment [S3]: Sentences repetition

Hyperlipidemia is well recognized as a major risk factor for the growth of GDM. Although, a few studies have addressed the effects of dietary fat on plasma lipids in pregnant women, however, there is no evidence that taking an FA supplement increases the chance of developing GDM.⁽⁹⁾

The ability of FA to prevent neural tube defects (NTDs) is widely documented. FA supplementation guidelines have been widely accepted before and throughout pregnancy globally. According to the World Health Organization (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 longer periods of time than the guidelines suggested. According to a recent Chinese poll, 48.8% of pregnant women used FA for more than 12 weeks prior to 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 mainly on the effect of high FA doses or varying periods of FA usage, but no studies have however, 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, especially on lipid metabolism or diabetes mellitus. Therefore, the basis of this analysis is to determine whether there was any relationship linking the length of FA supplementation with the risk of development of GDM.

To investigate if lipid profiles have a specific role in the link between pteroylglutamic acid supplementation with the risk of the development of GDM, our search focused on the relationship between supplementation duration and blood lipid profiles. Long-term FA supplementation, we hypothesized, would raise blood lipid profiles, thereby increasing the risk of GDM. ⁽¹²⁾ It is hope that this search might give new insight into the long-term negative effects of FA supplementation on GDM in Chinese women. Metformin works by lowering hepatic glucose synthesis and improving glucose excretion, so it is recommended 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 agents for T2D all over the globe. However, due to malabsorption, it lowers pteroylglutamic acid and cyanocobalamin levels while raising levels of homocysteine (Hcy). Metformin affects folate, B12, and Hcy levels, which is governed by the amount and duration of used. When methionine, an important amino acid, is demethylated, it produces homocysteine, a sulfur-containing aminoalkanoic acid.

Irregularities of endothelium, IR, prothrombotic condition, macro-angiopathy, diabetic nephropathy, dyslipidemia, oxidative anxiety, and sub-standard disorder management have all been associated with high Hcy levels in diabetics.⁽¹³⁾ The association of insulin resistance and plasma homocysteine levels has been a source of contention. In two important epidemiological studies, hyperhomocysteinemia have been found to be marginally but significantly correlated with insulin levels as well as insulin resistance. In individuals with impaired fasting glucose, fasting serum homocysteine was significantly higher.

In T2D, tHcy have been linked to an increased risk of the development of cardiovascular disorders as well as mortality. Elevated total homocysteine levels 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 levels may assist in minimizing cardiovascular diseases, as well as morbidity and mortality.

In one of two re-methylation processes, Hcy is able to re-methylate to methionine or trans-sulphurate to cysteine, with pteroylglutamic acid serving as a methyl contributor in both reactions. Furthermore, Hcy's vasculotoxic effect is thought to be mediated by a number of routes, the majority of which are associated with the loss of endothelium-regulating functions.⁽¹⁵⁾ Endothelial cell injury, reduced nitric oxide availability, oxidative anxiety, smooth muscle cell division, improved leukocyte adhesion, rapid platelet aggregation, insufficient fibrinolysis, and the establishment of a chronic inflammatory condition have all been linked to homocysteine-induced vascular disease.

Due to an affirmative relationship linking body weight with Hcy concentration and an approving knowledge on the effect of folic acid on parameters of glycemc control, insulin resistance, total cholesterol, TG, LDL-C, HDL-C, serum folic acid and cyanocobalamin, plasma homocysteine, a RCT was conducted to evaluate the impact of oral pteroylglutamic acid supplementation for eight weeks on parameters of fasting blood glucose, glycated hemoglobin (HbA1c), serum insulin, IR as well as total cholesterol.

Methodology

The key words "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 dependent 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. Despite the fact that 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 of the disease.** Increased **appetites, exhaustion, along with unhealed wound are also viable symptoms.** Usually, these symptoms manifest **themselves** moderately - heart disease, strokes, diabetic retinopathy, which can lead to blindness, renal failure, along with poor blood flow in the limbs. All of **these** 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 **is** the leading causes of type 2 diabetes. Some persons are genetically predisposed to **the** disease more than others.

Type 2 diabetes accounts for **about** 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 (**HbA1c**).

Vitamin B9, Folate or Folic Acid

The term folate refers to 150 pteroylglutamate 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 **study**, low folate and B-12 intakes were associated **with** 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 **also** been shown to aid persons with type 2 diabetes improve their **glycemic** control by reducing glycated hemoglobin (**HbA1c**), fasting blood glucose, serum insulin, IR, as well as homocysteinemia. Pyridoxine, folic acid, and cyanocobalamin supplementation **have in addition**, 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 **synthesize** DNA and RNA, as well as to **metabolize** 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 **levels of this** parameter 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 **utilize** 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 **myocardial infarction** (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 adequate **amount is not taken**. 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 **one** month if their diet is inadequate in **folate**. Total body folate levels in adults **ranged between** 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 published in 2019, it became the 89th most widely **used** 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 is well studied in the field of biochemistry. The word "pteroylglutamic acid" is **restricted to** the

produced version that is utilized as a dietary reserve, whereas "folic acid" refer to 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 **incidences** 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 **become** pregnant without intending to **do so**, or may not discover they are pregnant until far into the first trimester, which is the important period for minimizing the risk of NTAs. Countries have **both mandated voluntary dietary fortification of wheat flour and other grains**, or have none at all **or have** rely on public health and healthcare practitioner guidance to women of reproductive age. When mandated fortification was compared between nations with voluntary fortification **and those with none**, 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; 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 **levels of** folic acid, B12, and TAC, as well as **reduction** in plasma homocysteine and serum malondialdehyde.⁽¹⁸⁾ Homocysteine, is a sulfur-containing amino alcanoic acid, and is generated when the essential amino alcanoic acid, methionine is broken down.⁽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 a variety of factors.⁽²⁰⁾

At dosages as low as 0.5 mg/d, pteroylglutamic acid supplementation has been found 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

Despite the fact that vitamins have a substantial impact on diabetes mellitus risk, development, and consequences, there is insufficient evidence to recommend independent or combination of many different vitamins' supplementation in the diabetic population in most patients. Consuming a range of meals rich in vitamins in appropriate amounts is the greatest strategy to achieve healthy nutritional status. Dietary evaluations are crucial in this instance to discover specific consumption deficiencies and offer suggestions. Overdosing or toxicity is risk associated with supplement usage, particularly with regard to specific vitamins; these negative consequences are well described. Pteroylglutamic acid plasma parameters determine endothelium-mediated vasodilation in type 2 diabetic patients. These findings support the notion that pteroylglutamic acid has a direct influence on 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, as well as reduced IR in T2D patients. In T2D patients, use of high dosages of metformin, pteroylglutamic acid supplementation decreases plasma homocysteine levels along with improvement of glycemic control, insulin resistance, as well as folic acid and cyanocobalamin levels. This finding creates a safe and secure environment.

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