



Quatrefolic®
The 4th generation folate



active folate and glucose metabolism



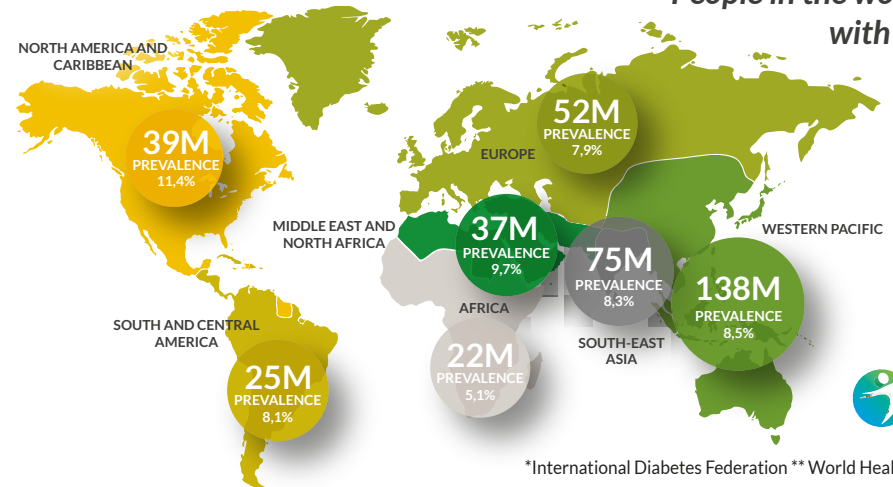
The global prevalence of IGT (Impaired Glucose Tolerance) was estimated at 7.3% of the adult population in 2017, equivalent to 352.1 million individuals. By 2045 the pervasiveness is anticipated to increase to **8.3% of the global adult population, equivalent to an estimated 587 million individuals.**

Prediabetes is a condition that can be considered an early, yet potentially reversible stage of the development of type 2 diabetes (15-30% of people with prediabetes will develop type 2 within 5 years).

Type 2 diabetes mellitus (T2DM) is on the rise worldwide. More than 400 million people were living with diabetes as of 2015* and 95% of people around the world that have Type 2 diabetes mellitus.**

The many risk factors for this type of diabetes include lifestyle decisions that result in excess body weight and physical inactivity. Consistent evidence shows that the **risk of developing type 2 diabetes mellitus can be reduced by adhering to a healthy diet with the right level of vitamins such as folate and regular physical activity.**

People in the world living with diabetes

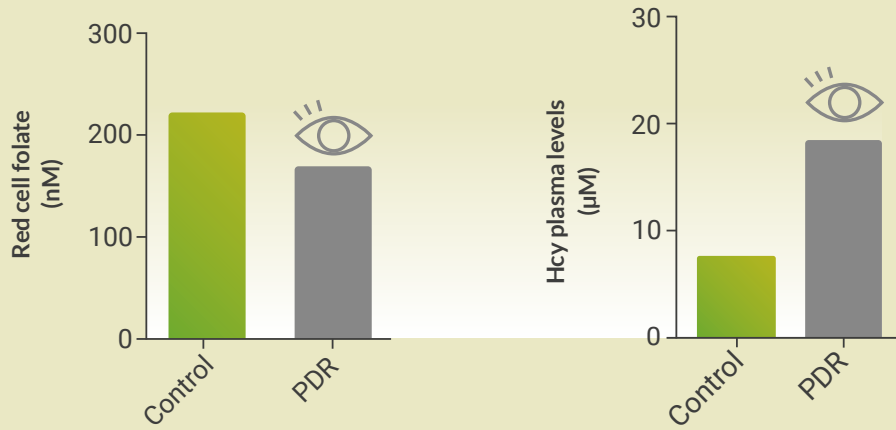


*International Diabetes Federation ** World Health Organization

Folate's Interconnection with Glycemic Control

There is a growing interest in the considerable benefits of the glycemic profile. In particular, folate supplementation (vitamin B9) might be beneficial for glucose homeostasis and lowering, insulin resistance (IR) with a possible role in diabetes deterrence, and reducing the risk of T2DM, and some diabetic conditions associated with it.

Recent studies have shown that circulating folate concentrations are significantly lower in T2DM patients compared with healthy individuals.



Adapted from Malaguarnera et al. Clin Ophthalmol. 2015

Lower levels of red blood cell folate, and increased Hcy level, were observed in patients with T2DM, especially with complications (PDR, proliferative diabetic retinopathy)

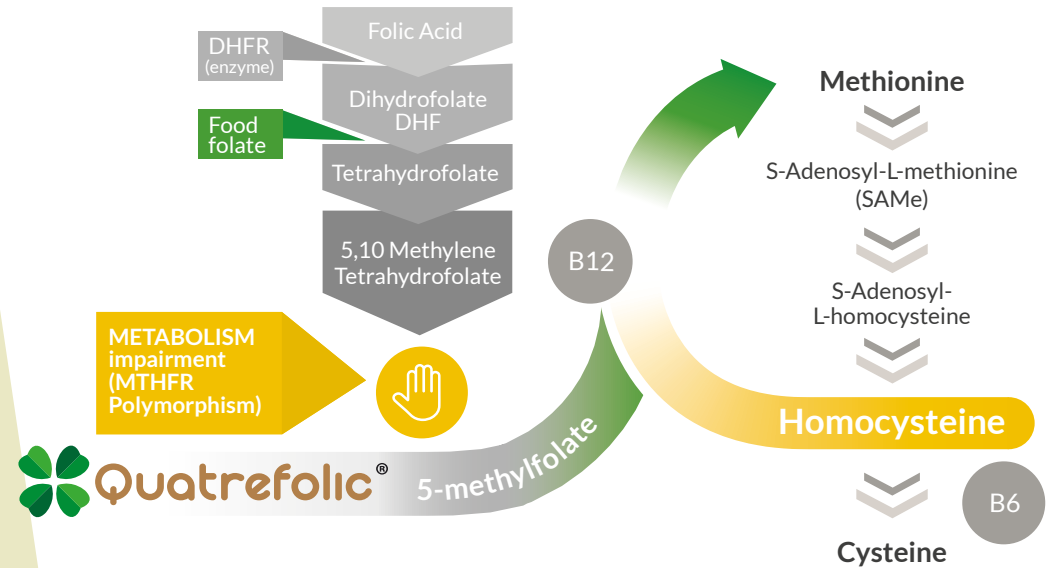
In a large prospective cohort study (2020), folate intake (including both dietary and supplemental resources) was inversely associated with the incidence of diabetes among American adults during a 30-year follow-up. Presumably, this inverse association is explained by the pathways of folate with mechanisms related to homocysteine (Hcy) levels, IR, and systemic inflammation.

Folate is crucial to one-carbon metabolism, a specific pathway that is essential for cellular function, amino acid metabolism, both DNA and RNA biosynthesis, DNA methylation, and methylation reactions.

Asbaghi O et al. Nutrients. 2021; Malaguarnera G. et al. Clin Ophthalmol. 2015; Genquan JMD et al. Asia Pac J Clin Nutr 2021; Kido Y. Diabetology International. 2017; Hayden MR et al. Medicina (Kaunas). 2021; Galicia-Garcia U et al. Int J Mol Sci. 2020; Eguchi, N. et al. Int. J. Mol. Sci. 2021; Shang Y et al. J Intern Med. 2019; Ling C et al., Diabetes. 2009.

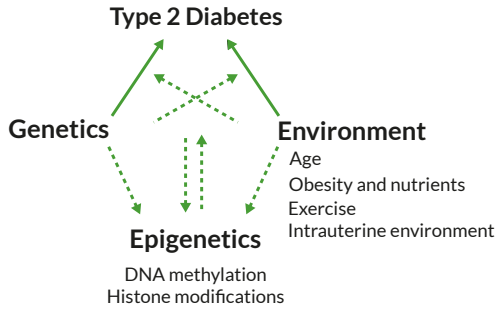
FOCM, Folate, and Diabetes

Folate enters the methionine cycle in the active form of 5-methyltetrahydrofolate (5-MTHF or methylfolate). Both food folate and folic acid need to be transformed to this active folate through a multistep enzymatic conversion, where the enzyme MTHFR plays a key role. MTHFR polymorphism prevalence in the general population is approximately 40%. Individuals can have low availability of 5-MTHF, independent of folic acid supplementation, with potential accumulation of Hcy in the blood, causing increased oxidative stress and vascular damage.



Quatrefolic® , glucosamine salt of the 5-methyltetrahydrofolate (5-MTHF or methylfolate), represents a natural-based approach to help manage glycemic problems, diabetes progression, and diabetes complications.

Folate's Interconnection with Glycemic Control



Adapted from Ling et al. Diabetes. 2009

T2DM is a metabolic disease characterized by high blood glucose, insulin resistance, and a relative lack of insulin. It is also associated with inflammatory profiles and altered DNA methylation patterns. Coexisting disorders, including obesity, hypertension, and dyslipidemia, contribute to the severity of T2DM.

This metabolic disease is characterized by a combination of two primary factors: **defective insulin secretion by pancreatic β -cells and the inability of insulin-sensitive tissues to respond appropriately to insulin.**

Defects in any of the mechanisms involved in these processes can lead to a metabolic imbalance responsible for the development of the disease.

Before people develop T2DM, they almost always have prediabetes—where blood glucose levels are higher than normal, but not yet high enough to be diagnosed as diabetes.

Early nutritional treatment as well as moderate lifestyle changes can actually return blood glucose (blood sugar) levels to a normal range, effectively preventing or delaying T2DM.

Benefits of folate supplementation

- ↑ Ameliorate DNA methylation
- ↑ Improve glycemic control
- ↑ Improve endothelial function
- ↓ Decrease inflammation and oxidative stress
- ↓ Reduce fasting blood glucose
- ↓ Reduce serum insulin
- ↓ Decrease insulin resistance

Asbaghi O et al. Nutrients. 2021; Malaguarnera G. et al. Clin Ophthalmol. 2015; Genquan JMD et al. Asia Pac J Clin Nutr 2021; Kido Y. Diabetology International. 2017; Hayden MR et al. Medicina (Kaunas). 2021; Galicia-Garcia U et al. Int J Mol Sci. 2020; Eguchi, N. et al. Int. J. Mol. Sci. 2021; Shang Y et al. J Intern Med. 2019; Ling C et al., Diabetes. 2009.

Natural history of Prediabetes in older adults

NORMOGLYCEMIA

PREDIABETES

DIABETES

REVERSION 22%

13% PROGRESSION

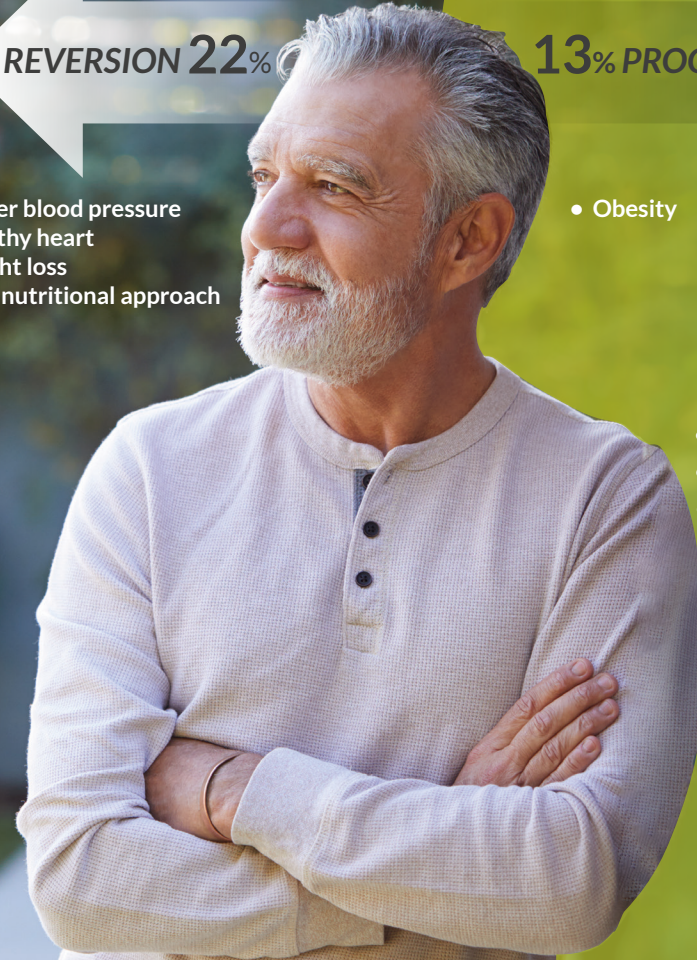
- Lower blood pressure
- Healthy heart
- Weight loss
- Good nutritional approach

- Obesity

COMPLICATIONS

- Diabetic Nephropathy
- Diabetic Retinopathy
- Diabetic Polyneuropathy
- Cardiovascular Risk
- Thrombosis Risk

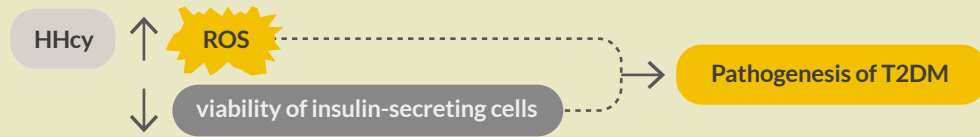
DIED 23%



Behind the mechanisms of T2DM and Folate

Hcy-Dependent Pathway

Folate deficiency contributes to elevated Hcy (HHcy) concentrations, a recognized risk factor for the development of cardiovascular disease and T2DM. In T2DM development, acute and prolonged exposure to HHcy has adverse effects on the cell viability of pancreatic β -cells.

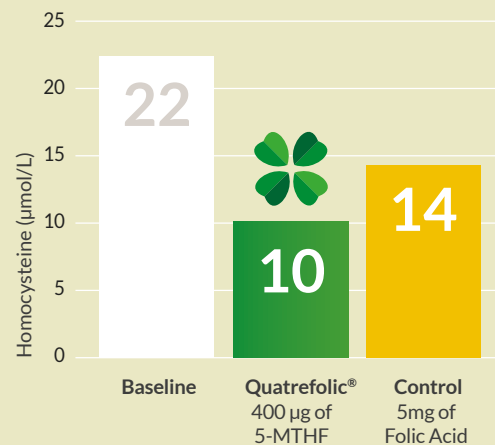


MTHFR enzyme is responsible for converting dietary folate into reduced active folate. Consequently, this enzyme is crucial for maintaining adequate levels of Hcy. MTHFR polymorphisms that affect this conversion may hence affect Hcy concentration. Although the results are still conflicting, a meta-analysis published in 2013 has investigated the **associations of MTHFR-linked Hcy and T2DM, providing evidence that polymorphic TT genotype of MTHFR C677T contributes to susceptibility to T2DM**, and supported the hypothesis that elevated Hcy is causally related to increased risk of T2DM.

Folate supplementation is widely accepted and recommended to any patient/person who has an elevated Hcy level for its normalizing effect.

The efficacy of Quatrefolic® (400 mcg plus B6 and B12) versus a conventional high-dose folic acid supplement (5 mg/day) has been evaluated in hypertensive subjects at low cardiovascular risk (104 patients with Hcys $\geq 15 \mu\text{mol/L}$).

The treatment was significantly effective with the ideal Hcys level reached in 55.8% of cases in the Quatrefolic® group, and it was significantly higher than in controls.

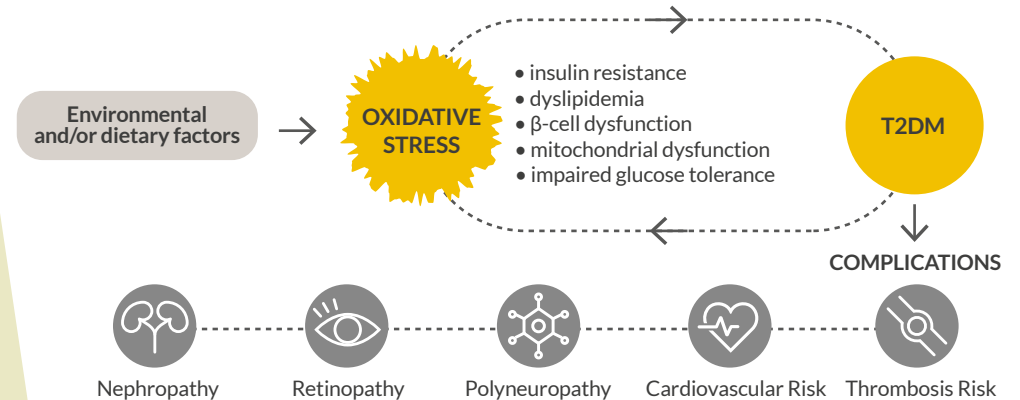


Hcy-Independent Pathway

Pancreatic β -cells are particularly susceptible to oxidative stress due to their high endogenous production of reactive oxygen species (ROS) and their low antioxidant capacity, suggesting that oxidative stress may play an important role in β -cell failure and death. If β -cell functioning is impaired, it results in the underproduction of insulin, fasting hyperglycemia, and eventually the development of T2DM.

On the other side, chronic exposure to a glucose-rich environment and consequent hyperglycemia can induce oxidative stress, creating several physiological and pathophysiological changes, exacerbating its toxic effect on cells, tissues, and organ systems.

As T2DM begins to develop, the body becomes less sensitive to insulin and the resulting IR also leads to inflammation. A vicious cycle can result, with more inflammation causing more IR and vice versa.



Folate is a well-known antioxidant molecule protecting cells from oxidative degradation. Additionally, the actions of folate in DNA methylation, repair, and synthesis processes may influence the inflammatory phenotype via epigenetic changes and modulation of cell proliferation.

Globally, folate supplementation seems to be able to significantly decrease fasting blood glucose, serum insulin, and insulin resistance.

T2DM and Complications: How Folate Can Help

Chronic hyperglycemia associated with diabetes can result in end-organ dysfunction and failure, and will trigger chronic metabolic syndrome, including obesity, cardiovascular disease, retinopathy, nephropathy, dyslipidemia, and hypertension. T2DM now represents a coronary heart disease risk, and nearly 80% of diabetic mortality is the result of diabetes-induced cardiovascular disease.

The increased risk of CVD in T2DM patients is associated with high Hcy levels that promote endothelial dysfunction and increase the likelihood of atherosclerosis development. T2DM with high Hcy levels are associated with increased incidence of venous thrombosis.

The antioxidant and anti-inflammatory properties of folate - in particular of Quatrefolic®, biological active form 5-MTHF not dependent on MTHFR action for activity - can contribute to combating the inflammation and the vicious cycle of T2DM-related disease aggravation. Specifically, folate can promote micro-vessel (diabetic retinopathy) and nerve growth (diabetic polyneuropathy).

Sudchada P et al. Diabetes Res Clin Pract. 2012; American Diabetes Association. Diabetes Care. 2009; Guo Y et al. Front Bioeng Biotechnol. 2020

40%
of people
with diabetes



Diabetic Nephropathy
Kidney-related complication

27%
of people
with diabetes



Diabetic Retinopathy
Commonly encountered
microvascular complication

10%
to 90%



Diabetic Polyneuropathy
Complication associated with
poorly controlled T2DM

2% to 4%
fold
increased risk



Cardiovascular Risk
A major cause of death and
disability among people
with diabetes

15%
VS 11%
non diabetic



Thrombosis Risk
Platelets use too much glucose
and are hyperactive, underlying
many vascular problems that
arise in diabetes.

T2DM COMPLICATIONS

ONSET AND PROGRESSION

Genetic factors, including polymorphism
↓folate intake
↓folate metabolism deficiencies
(MTHFR polymorphisms)

One-carbon-metabolism impairment
↓Nitric oxide
↓ B vitamins (folate)
↑ Hcy accumulation

- Nutrition, lifestyle, genetics, age, metabolic factors
- Diabetes duration
- Metabolic syndrome
- Inflammation
- Neuropathic ischemia

↑ Hcy accumulation

↑ oxidative stress
↑ Hcy accumulation
MTHFR 677 genotyping

ASSOCIATED RISK FACTORS:

- Folate deficiency
- Elevated Hcy



supplementation can
correct folate deficiency
and efficiently
reduce/normalize plasma
homocysteine levels

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Clement A. et al. J Gynecol Obstet Hum Reprod. 2020; Jacquesson J, Poinois L. et al. J Gynecol Women's Health 2017; Gayte OMB LE. et al. J Assist Reprod Genet 2019



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