KESANS : **International Journal Of Health and Science**
e-ISSN : 2808-7178, p-ISSN : 2808-7380
Web : http://kesans.rifainstitute.com/index.php/kesans/index

The Role of Folic Acid in Stroke Prevention

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Article Information
Accepted : **15 November 2021**
Submitted : **06 December 2021**
Online Publish : **20 December 2021**

Abstract
Stroke is one of the most serious health problems faced today. This is because a sudden stroke can cause physical and mental disabilities that can interfere with a person's productivity and can even cause sudden death. Stroke can be divided into two, namely hemorrhagic stroke and non-hemorrhagic stroke. Hemorrhagic stroke is a stroke that occurs due to damage to blood vessels in the brain. While non-hemorrhagic stroke, also known as ischemic stroke, occurs when the blood supply to the brain is interrupted or stopped. About 80% of the most common strokes are caused by an ischemic stroke. One of the causes of ischemic stroke due to atherosclerotic plaque. Elevated levels of homocysteine in the blood (hyperhomocysteinemia) can lead to chronic inflammation of the blood vessels that triggers the formation of atherosclerotic plaques and causes blockage of blood flow. Folic acid is a type of water-soluble vitamin and can play a role in preventing stroke. Folic acid can act as an antihomocysteine so that it can prevent the formation of atherosclerotic plaques which is one of the risk factors for stroke.
Keywords: Prevention of Stroke; Folic Acid; Homocysteine;

How to Cite
Alvin Anditya Almanda Zefanya, Mariska Dela Pebrianti/The Role of Folic Acid in Stroke Prevention. Vol. 1, No. 3, December 2021
DOI
https://doi.org/10.54543/kesans.v1i3.20
e-ISSN/p-ISSN
2808-7178 / 2808-7380
Publish by
Rifa'Isntitute

Introduction

Stroke is one of the health problems faced today, is the second leading cause of death and the third disability in the world. The global burden of the disease shows that globally, the risk of stroke has increased from 1 to 4 people (Usrin 2013). Meanwhile, in the United States, stroke is the third leading cause of death after cardiovascular disease and cancer. About 795,000 people in the United States have a stroke each year, about 610,000 having their first stroke. Stroke is also the cause of 134,000 deaths per year. The prevalence of stroke in Indonesia in 2018 states that the population aged > 15 years experienced a stroke by 10.9% or an estimated 2,120,362 people.

Two provinces with the highest prevalence of stroke in Indonesia are East Kalimantan Province (14.7%) and DI Yogyakarta (14.6%). Meanwhile, Papua (4.1%) and North Maluku (4.6%) had the lowest prevalence of stroke (Kemenkes RI, 2018). Stroke based on the cause can be divided into two, namely hemorrhagic stroke and non-hemorrhagic stroke or ischemic stroke. Hemorrhagic stroke occurs due to bleeding or disruption of blood vessels in the brain. Non-hemorrhagic or ischemic stroke can be caused by thrombus and embolism (Mubarani S, 2017). Arterial thrombosis is a complication of atherosclerosis that occurs due to a ruptured atherosclerotic plaque (Wijaya 2013). Atherosclerosis is inflammation of the blood vessels caused by endothelial dysfunction (Syaputra, Asni, and Malik 2014).

In the past, stroke only occurred in old age starting from 60 years old, but now starting at the age of 40 a person already has a stroke risk, the increase in stroke patients at a young age is more due to an unhealthy lifestyle (Laily 2017). Risk factors that cause stroke can be divided into factors that cannot be changed such as genetic factors, gender, and age. While the factors that can be changed are hypertension, unhealthy lifestyles such as smoking behavior, alcohol consumption and lack of physical activity (Suwaryo, Widodo, and Setianingsih 2019). An unhealthy lifestyle is often the cause of various diseases that attack the productive age. The younger generation often adopts unhealthy eating patterns by frequently eating foods high in fat and cholesterol but low in fiber. Excessive sugar consumption is also not good because it can cause obesity which results in a buildup of energy in the body (Listiyana, Mardiana, and Prameswari 2013). These things can increase the risk of atherosclerotic plaque, coronary heart disease and stroke.

Folic acid is a water-soluble vitamin and can be produced synthetically. Based on a study, folic acid consumption can reduce the incidence of stroke in hypertensive patients (Akhirul and Chondro 2019) Folate is found naturally in plants, such as dark green leafy vegetables. Folate plays a very important role in pregnancy and childhood for continued cell division and growth because it can be used to synthesize and repair Deoxyribonucleic Acid (DNA) (Listiyana, Mardiana, and Prameswari 2013).

Folic acid has also been found to play a role in preventing stroke due to its anti-homocysteine properties (Hankey 2018). Homocysteine is derived from the essential amino acid methionine, which is abundant in animal protein sources. High levels of homocysteine in the blood (hyperhomocysteinemia) are associated with an increased risk of heart disease and stroke.

Homocysteine is an amino acid formed from the demethylation of methionine (Tangkilisan and Rumbajan 2016). Methionine is converted to homocysteine via the intermediate S-adenosylmethionine, which acts as a methyl donor. The nature of folic acid as an antihomocysteine can inhibit the formation of atherosclerotic plaques which is a risk factor for stroke (Liew 2016).

Method

Literature review is research conducted by researchers by collecting a number of books, magazines related to problems and research purposes. This technique is carried out with the aim to reveal various theories that are relevant to the problem being faced / researched as a reference material in the discussion of research results.

Results and Discussions

1. Folic Acid

Comes from the Latin word meaning leaf. Folic acid or also known as folate, folacin, vitamin B9, acifolic, folcidin, and scientifically as pteroylglutamic acid is a water-soluble vitamin, can be produced synthetically, and can also be found in foods and supplements. Folic acid is the parent compound of a group of compounds commonly known as folate. This compound has a molecular weight (BM). The folic acid molecule consists of three groups, namely pteridine, a ring containing a nitrogen atom, a psoriasis aminobenzoic acid (PABA) ring and glutamic acid. The human body cannot synthesize the structure of folate, so it requires external intake, namely food (Tangkilisan and Rumbajan 2016). Folic acid has an important role in preventing health problems such as megaloblastic anemia and neural tube defects (NTD). Chronic folic acid deficiency can increase the risk of cognitive decline, depression, neuropathic disorders and cancer (Sobczy ska-Malefora and Harrington 2018).

Folate also plays an important role in preventing heart disease and stroke. Folate is an important cofactor in metabolic pathways that facilitate methylation reactions, as well as the formation and biosynthesis of DNA (Stanger 2002). Folic acid plays an important role in this by lowering homocysteine levels. Based on a study conducted on smokers, it was shown that folic acid supplementation in a 4-week trial could significantly reduce homocysteine and fibrinogen concentrations compared to placebo (Mitu et al. 2020). Folate content in the body is estimated to be around 10 mg to 30 mg. Normal serum total folate levels are about 5 to 15 ng/mL. Normal folate levels in erythrocytes range from 175 to 316 ng/mL. Higher concentrations of folate are stored in the liver, some in the blood and tissues. Folic acid deficiency occurs when folate levels are below 5 ng/mL (Liew 2016).

2. Sources of Folic Acid

Can be found in green plants such as broccoli, asparagus, citrus fruits (oranges, grapefruit, strawberries), nuts, avocados, peas, cabbage, beans, cauliflower, corn, celery, carrots, and squash. . In addition, folate can also be found in meat products such as

chicken, turkey, lamb, and beef. Folic acid can also be found in processed daily food products such as cereals, pasta, flour, and bread. In addition, there are also folic acid supplements that are sold freely in tablet or powder form (Liew 2016). The recommended consumption of folate in Indonesia starts from infants and children as much as 0.4 - 2 mcg/day, men and women are aged 10 -12 years as much as 3.5 mcg/day, men and women aged > 12 years as much as 4 mcg/day, and 4.5 mcg/day in pregnant women (RI MK, 2019).

Folate concentrations are usually determined in plasma, serum, and red blood cells. Folate deficiency is considered the most common vitamin deficiency in developed countries. This is due to modern food handling and processing. For example, when wheat is processed into flour, up to 90% of the oil, vitamins, minerals, phytochemicals, and fiber are removed [56]. In addition, folate is sensitive to heat exposure. As a result, much of the folate content in food is lost during transport, storage, and cooking. With so many modern processed foods, it is difficult for most people to meet their nutritional needs without supplements. Low folic acid intake and increased folate requirements with age may affect certain groups at risk for suboptimal folate intake such as the elderly, sick people, pregnant women, and children (Stanger 2002).

3. Metabolism of Folic Acid Folic

Acid, when taken as a supplement, is absorbed rapidly, especially in the proximal part of the small intestine through passive diffusion. Monoglutamate is then reduced to tetrahydrofolate (THF) in the liver and converted to the methyl or formyl form before entering the bloodstream. Folate is usually found in the bloodstream as 5-methyl-tetrahydrofolate (Liew 2016). Methionine is converted to homocysteine with the help of intermediate S-adenosylmethionine, which acts as a methyl donor. Homocysteine (Hcy) can be converted back to its initial form, namely methionine, or can be converted into cysteine by transsulfuration (Hankey 2018).

Folic acid that has been absorbed is transported to the liver and bone marrow and will be excreted through bile and urine. Although folic acid is quite easy to obtain, there are several things that make a person experience folic acid deficiency such as increased demand for pregnant women and lactation, due to drugs, genetic influences, enzyme deficiency, environmental factors and inadequate diet (Lestari 2019).

4. Hyperhomocysteinemia

Homocysteine (Hcy) is an amino acid that is the intermediate product of the biosynthesis of the amino acids methionine and cysteine. In plasma, homocysteine is divided into reduced (homocysteine) and oxidized (homocysteine) forms. Homocysteine metabolism involves major enzymes such as S-adenosyl-L-methionine (SAM) synthetase/L-methionine adenosyltransferase, methyltransferase (MT), and S-adenosyl-Lhomocysteine (SAH) hydrolase. Homocysteine will undergo remethylation to form methionine through several pathways.

The first pathway requires vitamin B12 and folate cofactors. Folate acts as a cofactor for N-5-methyl tetrahydrofolate (THF) which will donate a methyl group to homocysteine in a reaction catalyzed by the enzyme N-5-methyl tetrahydrofolate (THF). The second pathway uses betaine which is synthesized by choline by betaine-homocysteine methyltransferase (BHMT). Therefore, low folic acid levels cause homocysteine remethylation disorders, so that homocysteine cannot be converted to methionine and leads to the accumulation of homocysteine. In the end, it will result in an increase in homocysteine levels in the blood (hyperhomocysteinemia) (Lestari 2019; Suwanto 2017).

Hyperhomocysteinemia has been reported as a risk factor for atherosclerosis and coronary artery disease (Astoni and Irawan 2013). When compared with healthy individuals, forty percent of patients with coronary artery disease, cerebral or peripheral artery disease were found to have high plasma homocysteine levels (Welch and Loscalzo 1998). Hyperhomocysteinemia or high plasma homocysteine is defined as a level higher than 16 micromoles/L (Liew 2016). Hyperhomocysteine can be caused due to genetic mutations of the enzymes involved and environmental factors. The genetic mutation referred to here is a negative effect on the gene encoding the 5,10-methylenetetrahydrofolate reductase (MTHFR) enzyme synthesis, methionine synthase, and cysteine synthase, which are key enzymes for homocysteine metabolism. Blood (Suwanto 2017).

Methylenetetrahydrofolate reductase (MTHFR) plays an important role as an enzyme in folate metabolism. For homocysteine to be remethylated to methionine, a methyl donor such as 5-methyl tetrahydrofolate is required, which is produced from 5,10-methylenetetrahydrofolate in the reaction catalyzed by 5,10-MTHFR (Hankey 2018). Hyperhomocysteinemia can also be caused by environmental factors. Levels of vitamins B6, B12, and folic acid are inversely proportional to homocysteine levels. The role of these vitamins can be used as a therapy to reduce homocysteine levels (Suwanto 2017).

Hyperhomocysteinemia in the long term can cause the walls of blood vessels to become uneven and rough resulting in plaque formation. If it occurs continuously and thoroughly, atherosclerosis will occur. Plaque that occurs and continues to grow can become a thrombus that can trigger a stroke (Lumanau 2003). Maximum reduction in plasma homocysteine concentration can be achieved with a minimum dose of 0.8 mg/day of folic acid. Strain et al study found that giving vitamin B12 at a dose of 0.5 mg/day and vitamin B6 at a dose of 16.5 mg/day would reduce homocysteine concentrations by 7%, and when added with folic acid, it would reduce homocysteine concentrations by 25% (Muhi, Oenzil, and Izzah 2018).

5. Stroke Prevention

B vitamins (folic acid, vitamin B6, vitamin B12) can also be used as therapy to prevent strokes that appeared more than 15 years ago after the initial case. Epidemiological studies report an association between high plasma total homocysteine concentrations (tHcy) and incidence of cardiovascular disease (Hankey 2018).

Plasma THcy reflects both free-bound and protein-bound homocysteine, dimeric homocysteine and mixed cysteine-homocysteine disulfide (Hankey 2018). Hcy plays a role in causing atherosclerosis in four ways, namely increasing the proliferation of vascular smooth muscle cells, damaging the arterial endothelium, interfering with clotting factors and LDL oxidation (Dewayani 2007). Atherosclerosis is one of the factors that cause stroke (House and Urquhart 2015; Pajri and Safri 2018).

A systematic review of observational studies (cohort and case-control) demonstrated a strong, positive and dose-related relationship between serum tHcy concentrations and risk of stroke, regardless of other vascular risk factors. 6 7 A 3 mol/L increase in tHcy was associated with an increased risk of stroke of about 24% and an increased risk of myocardial infarction of about 15% (Hankey 2018). Folic acid supplementation has been shown to improve endothelial dysfunction in asymptomatic subjects with hyperhomocysteinemia (Stanger 2002).

Conclusion

The incidence of stroke is still high, and is still the second leading cause of death worldwide, making strokes need to be watched out for so that stroke prevention needs to be done as early as possible. Folic acid is a form of water-soluble vitamin and plays an important role in the body. Epidemiological studies report an independent triangular relationship between the MTHFR genotype, high plasma homocysteine (tHcy) levels may increase the risk of stroke. Based on a research study, folic acid (vitamin B9) can function as an antihomocysteine by lowering tHcy so that it can prevent the occurrence of atherosclerotic plaque which is a risk factor for stroke.

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