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CASE REPORT

Role of folic acid supplementation in level of c-reactive protein in metabolic syndrome : evidence based case report

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Abstract

Introduction: The prevalence of metabolic syndrome is increasing, its progression involves an inflammatory response that has an important impact on the initiation, progressivity, and complications of several diseases such as heart disease, stroke, type 2 diabetes mellitus, and cancer. C-reactive protein (CRP) is one of the inflammation markers increased in patients with metabolic syndrome. Folic acid has a role in metabolizing homocysteine and improving endothelial function. There have been many studies conducted, but the results are still inconsistent.

Method: Literature searching was conducted using PubMed, Cochrane Library, and Embase databases. MeSH terms, advanced search and eligibility criteria were used for title/abstract screening before journal review.

Results: One systematic review and meta-analysis (SR-MA) and one RCT met the PICO and eligibility criteria. The SR-MA found that folic acid administration can reduce CRP level (WMD -0.94 (95% CI -1.56 – 0.32; p=0.00) at a dose of 0.15 mg/day for 12 weeks to 10 mg/day for 2 weeks, while the RCT found an insignificant result.

Conclusion: Folic acid supplementation has a potential benefit to decrease CRP levels in metabolic syndrome.

Keywords: folic acid, supplementation, CRP, metabolic syndrome, case report

Case Scenario

A 34-year-old woman came to clinical nutrition clinic for post-hospitalization consultation with diagnosis of Grade II Obesity in Mirizzi syndrome post laparotomy cholecystectomy adhesiolysis, common bile duct (CBD) exploration, bypass choledochoduodenostomy POD-11. The patient now has no complain, fever is absent, intake and toleration of oral route was good, hemodynamics was stable with blood pressure 134/77 mmHg, heart rate was 90 times per minute, respiratory rate was 20 times per minute, and temperature was 36.8^{o}C. On physical examination of abdomen, it found distended, intestinal noise within normal limits, tenderness is absent, in right hemiabdomen surgical wound looks clean and dry. On physical examination of extremities, no edema or muscle wasting was obtained. Anthropometric examination obtained the weight was 93 kg, height was 165 cm, waist circumference was 105

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cm. From laboratory examination it obtained that leucocyte was 9.300/µL, CRP 5.6 mg/L, triglyceride 155 mg/dL, HDL cholesterol 37 mg/dL, and fasting blood glucose was 110 mg/dL. The patient was given nutritional medical therapy of 1700 kcal according to total energy needs. Patients asked about recommended folic acid supplementation to support in reducing inflammation with metabolic comorbidities.

Introduction

Metabolic syndrome is still one of the main health problems. From 1999 to 2014, the prevalence of metabolic syndrome in US increased from 27.6% to 32.3% with mortality rate dropped dramatically from 29.6% to 2.7% owing to advances in health care.[1] Data in Indonesia shows similarities in prevalence with rate of 28% in men and 46% in women in 2020, but very different mortality with rate of 73%.[2,3]

The pathophysiology of metabolic syndrome involves an inflammatory response, which has an important impact on the initiation, progression, and complications of several diseases such as heart disease, stroke, type 2 diabetes mellitus and cancer. [4] C-reactive protein (CRP) as one of the acute phase proteins of inflammatory markers increases and can predict new or recurrent events in patients with metabolic syndrome. The inflammatory marker CRP has been widely used in epidemiological and interventional studies to assess and identify associations between systemic inflammation and metabolic syndrome.[5]

Folic acid has shown effect on decreasing homocysteine levels, improving endothelial function, and decreasing inflammatory reactions. A study conducted by Talari et al.,[6] in 2016 showed that folic acid can reduce CRP levels in patients with type 2 diabetes mellitus. However, a study from Spoelstra et al.,[7] in 2004 showed that supplementation of folic acid for 6 months did not improve CRP level in patients with type 2 diabetes mellitus. This difference creates uncertainty regarding the effect of folic acid on inflammatory response in patients with metabolic syndrome.

Therefore, the authors are interested in finding more information about the relationship between folic acid and inflammatory markers in patients with metabolic syndrome, in the hope of providing recommendation on the management of metabolic syndrome. This study aimed to assess the effect of folic acid supplementation on inflammatory marker of CRP in patients with metabolic syndrome. Because serum CRP level can be reflected by high sensitivity-CRP (hs-CRP) in clinical practice, this critical study included studies using hs-CRP as an outcome.[8]

Clinical question

P: Adult patients with metabolic syndrome

I: Folic acid supplementation

C: Without folic acid supplementation

O: Level of CRP

Clinical question:
could folic acid supplementation decrease the level of CRP in patients with metabolic syndrome?

Methods

Literature search was performed using combination of MeSH terms and Title/Abstract on three large databases: PubMed, Cochrane Library and Embase. Searching was carried out on 4th January 2024. The keywords used were "folic acid", "supplement", "C reactive protein" and "metabolic syndrome" (**Table 1**). Critical assessment tools and levels of evidence are based on the Oxford Center for Evidence-Based Medicine.

After obtaining the articles, filtering of duplication is carried out. If search results are found as SR-MA of RCT, the reviewer will exclude RCT that are included in the SR-MA to avoid duplication. The articles obtained are then selected by comparing the title and abstract with the PICO from predetermined clinical questions and with other eligibility criteria. After getting relevant articles then proceed with critical review by discussing with senior writers.

Table 1. Resources and Search Strategy

Database	Terminology	Hits	Eligible
PubMed	(("folic acid"[MeSH Terms] OR "folic acid"[Title/Abstract]) AND ("c reactive protein"[MeSH Terms] OR "c reactive protein"[Title/Abstract]) AND ("metabolic syndrome"[MeSH Terms] OR "metabolic syndrome"[Title/Abstract])) AND (randomizedcontrolledtrial[Filter] OR systematicreview[Filter])	4	2
Cochrane	#1 (metabolic syndrome):ti,ab,kw #2 (folic acid supplementation):ti,ab,kw #3 (CRP):ti,ab,kw #4 #1 #2 AND #3	6	1
Embase	#1 (metabolic syndrome):ti,ab,kw #2 (folic acid supplementation):ti,ab,kw #3 (CRP):ti,ab,kw #4 #1 #2 AND #3 #5 #4 AND ('meta analysis'de OR 'randomized controlled trial'/de OR 'systematic review'de)	3	1

Eligibility Criteria

Inclusion criteria including research with SR-MA of RCT dan RCT design, subjects over 18 years of age with metabolic syndrome, received folic acid supplementation, and the outcome was level of CRP. Exclusion criteria including animal study, article not available in full text and was written in other language than English and Indonesian.

Results

As shown in **Figure 1**, one SR-MA of RCT and one RCT were included in this Evidence-Based Case Report. Based on the criteria of the Oxford Centre for Evidence Based Medicine, the level of evidence of both articles is level 1. The subjects in both articles were adult patients with metabolic syndrome and received folic acid supplementation in the intervention group compared with no folic acid supplementation in the control group, to assess CRP level as the outcome.

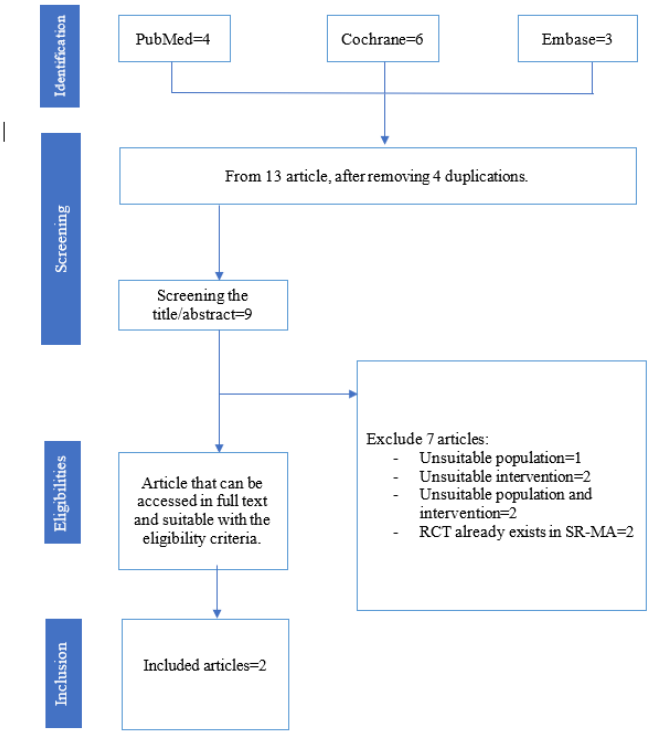

Figure 1. Prisma's Flow Chart

Critical appraisal

In the article by Jiang Z et al.[8], the authors assess using FAITH tools, while in the article by Schneider MP et al.,[9] the authors assess using CEBM tools from the University of Oxford. Before critical appraisal, an assessment of the relevance of the two articles to the clinical question using PICO was carried out. The articles obtained have good relevance to the established clinical question, namely the effect of folic acid supplementation on CRP level in adult patients with metabolic syndrome. This can be seen in

Table 2. Study Characteristic

Author	Study design	Population characteristic	Intervention	Outcome
Jiang Z, et al.,[8]	SR-MA of RCT	A total of 10 studies with a total of 511 patients. Adult patients (≥18 years old) with metabolic syndrome (with several conditions including overweight, obesity, PCOS, CAD, T2DM, and CHD).	Folic acid supplementation was given at a dose of 0.15 mg/day for 12 weeks up to 10 mg/day for 2 weeks, with 2 studies including vitamin B6 or B12 supplementation compared with placebo.	All studies had CRP/hs-CRP outcomes, 5 studies have variation in outcome (including other inflammatory markers in the form of IL-6 and/or TNF-α).
Schneider MP, et al.,[9]	Double-Blind RCT	A total of 75 adult male subjects (≥ 18 years old) with BMI > 25 kg/m^2.	Folic acid supplementation at a dose of 5 mg/day orally for 4 weeks.	The outcomes in this study consisted of: 1) inflammatory markers in the form of hs-CRP, IL-1β, and adiponectin; 2) oxidative stress markers in the form of GSH/GSSG ratio and total antioxidant capacity; 3) vascular tone in the retina and kidneys.

SR-MA, systematic review meta-analysis; RCT, randomized controlled trial; PCOS, polycystic ovarian syndrome; CAD, coronary arterial disease; T2DM, type 2 diabetes mellitus; CHD, chronic heart disease; hs-CRP, high sensitive C reactive protein; IL-6, interleukin-6; TNF-α, tumor necrotizing factor- α; BMI, body mass index; GSH/GSSG ratio, glutathione/oxidized glutathione ratio.

Table 3. Relevance Criteria

Authors	Population similarity	Determining Factor similarity	Outcome similarity
Jiang Z et al. (2022)	+	+	+
Schneider MP et al. (2011)	+	+	+

Table 3. However, there are several variations, such as variations in intervention in the SR-MA by Jiang et al.,[8] where two studies included vitamin B6 or B12 supplementation. In addition, there are variations in outcomes of the two studies with varying outcome including IL-6 and/or TNF-α. The outcomes in study by Schneider[9] had a variety including IL-1β, adiponectin, GSH/GSSG ratio, NOS-dependence vascular tone, dan total antioxidant capacity.

From a critical appraisal of the two articles, an assessment of validity was obtained. Article by Jiang Z et al.,[8] evaluated the risk of selection bias, performance bias, detection bias, and reporting bias in the studies included, and found that most of it had an unclear risk of bias (67,9%), followed by a low risk of bias (28,6%) and high bias (3,5%) in performance bias, where there were 2 studies conducted open label. Publication bias was assessed using funnel plots, Egger's test, and Begg-Mazumdar correlation test, and the result showed no publication bias. Meanwhile, in the article by Schneider MP et al.,[9] good validity was obtained, where randomization was carried out and the randomization list was sealed, research subjects were monitored for quite a long time and in detail, folic acid level were measured to ensure compliance with the intervention, subject did not know who received treatment and who received placebo, treatment beside the intervention in both groups was the same and comparable from the start of the trial where folic acid level were almost the same in both groups, and also all subjects involved taken into account in the final conclusion. Summary and details of the critical appraisal can those two articles can be seen in **Table 4, 5, and 6** below.

Table 4. Summary of Critical Appraisal of Validity, Importance, Applicability dan Level of Evidence (SR-MA) Criteria

	Questions	Jiang Z et al.,[8]
Validity	Does the SR-MA describe the clinical question (PICO) and is it used in article search and selection?	+
	Did the search uncover all relevant evidence?	+
	Have the selected studies been critically appraised?	+
	Does it only include high-quality studies?	-
	Are study results summarized in tables and diagrams and heterogeneity between studies assessed?	+
Importance	Do the research results have a big influence, and are they not due to chance?	+
	Are clinically important results statistically significant?	+
Applicability	Are the characteristics of the patients we will be dealing with similar to the characteristics of research patients?	+
	Are the exposures in the study similar to those in our patients?	+
	Level of evidence	1

Table 5. Summary of Critical Appraisal of Validity, Importance, Applicability dan Level of Evidence (RCT) Criteria

	Questions	Schneider MP et al.,[9]
Validity	Is patient therapy assigned randomly?	+
	And were the two groups similar at the start of treatment?	+
	Besides the treatment allocated, were both groups treated the same?	+
	Are all patients taking part in the trial counted? And were they analyzed in randomized groups?	+
	Are measurement objective or do patients and physicians remain blind to the therapy received?	+
Importance	How big is the impact?	The mean difference in intervention group was 0.3 and the control group was 0.6.
	What measurements are used, and what do they mean?	Mean difference in CRP level
	How precise are estimates of therapeutic effects?	Not statistically significant
Applicability	Can the study results help treat patient being treated?	+
	Is this treatment feasible in clinical practice?	+
	Do the potential benefits of therapy outweigh the potential harms of therapy for the patient being treated?	+
	Level of evidence	1

Literature 1: Jiang Z, Qu H, Chen K, Gao, Z. Beneficial Effect of Folic Acid on Inflammatory Markers in the Patient with Metabolic Syndrome: Meta-analysis and Meta-regression of Data from 511 Participants in 10 Randomized Controlled Trials. Critical Reviews in Food Science and Nutrition. 2022; 1-10.[3]

A. How well was the research done? **(INTERNAL VALIDITY)**

Question Does the systematic review address a focused question (PICO)?
The article: Yes ■ No ☐ Unclear ☐
Comment: In the title, abstract, and introduction, the authors have clearly stated the focus of the question under study, which consists of an intervention of providing folic acid supplementation, clinical outcome in the form of level of CRP (with variations of IL-6 and/or TNF- α), in the population metabolic syndrome patients (with variations of PCOS, CAD, stable CHD, and type 2 DM).
… and use it to direct the search and select articles for inclusion?
The article: Yes ■ No ☐ Unclear ☐
Comment: In the methods section, the authors explain the inclusion and exclusion criteria in accordance with the PICO mentioned above, with a clear definition of the population, and if there is uncertainty about the population in the study, a search is carried out to the authors of the RCT.
F Did the search find all the relevant evidence?
The article: Yes ■ No ☐ Unclear ☐
Comment: In the methods section, the authors state that a search was carried out in four databases, and identification and selection of studies according to eligibility criteria, resulting in 10 studies. The author will try to correspond to the experts if there are studies whose articles are unpublished. Apart from the narrative, this is also explained in the form of a flowchart.
A Have the studies been critically appraised?
The article: Yes ■ No ☐ Unclear ☐
Komentar: Dalam bagian metode, disebutkan penilaian kualitas metodologi studi dengan menilai ada atau tidaknya bias seleksi, bias performa, bias deteksi, dan bias *reporting*.
I Did they only include high quality studies?
The article: Yes ☐ No ■ Unclear ☐
Comment: There was a 3.5% high risk of bias from the risk of bias assessment of all studies, namely performance bias, where there were 2 studies conducted open label.
T Have the results been totalled up with appropriate summary tables and plot?
The article: Yes ■ No ☐ Unclear ☐
Comment: In the result section, the authors of this article display a summary of the data on the characteristics of the included studies in tabular form and the results are displayed in the form of a forest plot according to the outcomes of CRP, hs-CRP, and other variations in outcomes (IL-6 and TNF-α).
H … and heterogeneity between studies assessed and explained?
The article: Yes ■ No ☐ Unclear ☐
Comment: The author assessed and explained the heterogeneity of studies within the forest plot, namely that heterogeneity was found to be 46.34% between studies (heterogeneity $\chi 2=1.86$, p=0.03, I2=46.34%).

B. What were the results? **(IMPORTANCE)**

What measure was used, how large was the effect (could it have been due to chance)?
In this study, the weight-mean difference was -0.94 (95% CI -1.56, -0.32; p=0.00). Based on these results, it can be interpreted that the effect of folic acid supplementation on CRP is clinically important and statistically significant and not due to chance.
How are the results presented?
The author presents the pooled results in the form of a forest plot.

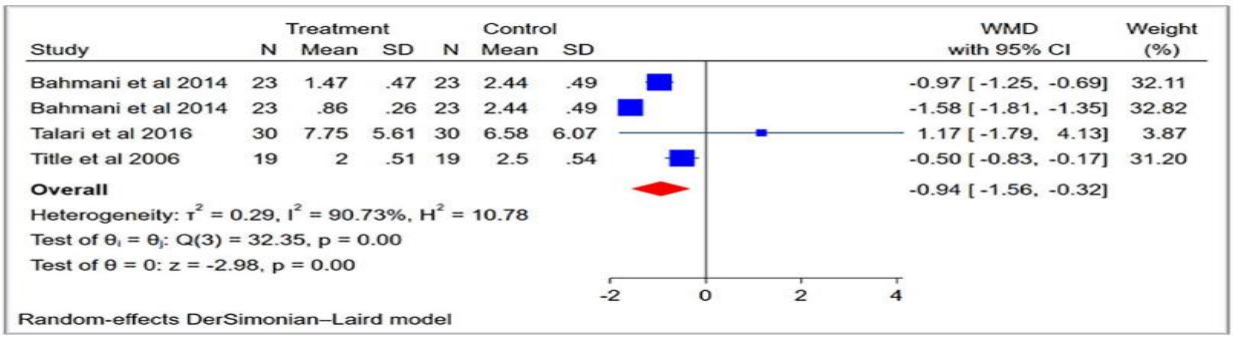

Figure 3. Forest plot for inflammatory marker hs-CRP

Are the clinically important result statistically significant?
Yes, the pooled result shows p = 0.00.

C. Can it be applied? **(APPLICABILITY)**

Are the clinical results applicable to our patients?	
Do the characteristics of the patients encountered resemble the characteristics of the research patient.	Yes, the patients encountered resemble the characteristics of research patients, namely patients with metabolic syndrome. Meanwhile, for other disease variations, the scenario patient has a history of multiple cholelithiasis (Mirizzi syndrome) post-operatively.
Are the exposures in the study similar to those in our patient?	Yes, folic acid supplementation has been applied to our patient.

Literature 2: Schneider MP, et al. Folic Acid Treatment Normalizes NOS-Dependence of Vascular Tone in the Metabolic Syndrome. Obesity; 2011; p. 963.

A. Are the results of this test valid? **(VALIDITY)**

R Was the assignment of patients to treatments randomized?
The article: Yes ■ No ☐ Unclear ☐
Comments: In the methodology section of the study protocol, it is stated that patients were devided into 2 groups, namely a group with metabolic syndrome and a group without metabolic syndrome, and then given therapy randomly between receiving folic acid and placebo for 4 weeks, paused with a wash out phase for 4 weeks between 2 therapy phase, which was carried out blindly.
R Were the groups similar at the start of the trial?
The article: Yes ■ No ☐ Unclear ☐
Comment: In the methods section, the authors explain the inclusion and exclusion criteria according to the PICO mentioned above, with a clear definition of the population. Metabolic syndrome is defined according to the US NCETP III guidelines which require a minimum of 3 of 5 criteria (WC > 102 cm, TGA ≥ 150 mg/dl, SBP ≥ 130 mmHg or DBP ≥ 85 mmHg, HDL < 40 mg/l, and FBG ≥ 100 mg/dl). Only male subjects were included because it was previously known that gender influences the outcome of endothelial function which is a variation in outcomes in this study apart from inflammatory markers. Other exclusion criteria were type 1 or 2 DM, kidney disease, liver disease, heart disease (myocardial infarction, coronary intervention, stroke, or peripheral vascular disease, or therapy with any antihypertensive, antidiabetic or antilipid). In addition, the characteristics of the two groups were summarized in a table, where there were no significant differences in the item age, weight, body surface area, body mass index, total cholesterol levels, LDL cholesterol, uric acid, creatinine, and urinary albumin excretion, as well as baseline folic acid levels.

A Aside from the allocated treatment, were groups treated equally?
The article: Yes ■ No ☐ Unclear ☐
Comment: Both groups were given a washout phase of the same duration, namely 4 weeks, and their baseline folic acid levels were also checked in both groups.
A Were all patients who entered the trial accounted for? And were they analyzed in the groups to which they were randomized?
The article: Yes ☐ No ☐ Unclear ■
Comment: In the result section, there is no mention of the number of subjects who took part on the final calculation or any information about loss to follow up, it is only stated directly in its entirety that the results showed no differences in inflammatory markers (including CRP) between the two groups. In the method section, it is stated that the subjects were analyzed in randomized group.
M Were measures objective or were the patients and clinicians kept "blind" to which treatment was being received?
The article: Yes ■ No ☐ Unclear ☐
Comment: In the method section, it is stated that measurements were carried out equally in both groups, and therapy was administered blindly (folic acid or placebo).

B. What were the results? **(IMPORTANCE)**

How large was the treatment effect?
In this study, the results were not significantly different between the two groups (therapy and control groups). The mean difference between the therapy group was 0.3 (CI 95%, p = 0.35) and the control group was 0.6 (CI 95%, p = 0.62).

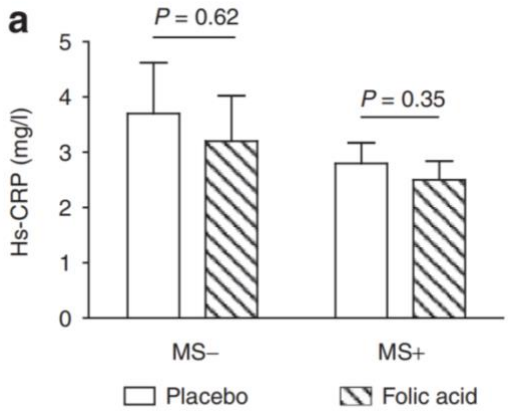

Figure 4 (**a**) High-sensitivity C-reactive protein (hs-CRP), (**b**) interleukin-1β (IL-1β), and (**c**) adiponectin levels in obese subjects with (MS+) and without (MS−) the metabolic syndrome during placebo (empty boxes), and folic acid treatment (shaded boxes).

What is the measure? What does it mean?
The author did not directly mention the mean difference between the two therapy and control groups. The result data is presented in the form of a bar chart as above without mentioning the absolute number of the average hs-CRP level. Therefore, in this critical appraisal the author read the hs-CRP levels based on the bar diagram presented, where the average hs-CRP levels in the group that did not have metabolic syndrome who were given placebo and folic acid each was 3.8 mg/l and 3.2 mg/l, while in the group with metabolic syndrome given placebo and folic acid, hs-CRP levels were 2.8 mg/l and 2.5 mg/l, respectively. From this data it can be concluded that the mean difference in the group that does not have metabolic syndrome is 0.6 mg/l and is greater than the group that has metabolic syndrome, namely 0.3 mg/l. However, the P value in each group was > 0.05, which means the value is not statistically significant.
How precise was the estimate of the treatment effect?
In this study, p>0.05 was obtained in both groups, so it can be concluded that the results of the two mean differences were not statistically significant.

C. Will the result help me in caring for my patient? **(EXTERNAL VALIDITY/APPLICABILITY)**

Could the results of the study help treat case patients?	
Is my patient so different to those in the study that the results cannot apply?	No, the characteristics of the patients in the study resembled the case patients, namely having metabolic syndrome.
Is the treatment feasible in my setting?	Yes, administering folic acid can be done and is easy to obtain in clinical practice for case patients.
Will the potential benefits of treatment outweigh the potential harms of treatment for my patient?	Yes, folic acid has potential benefits in reducing CRP levels. It has high toxic levels, and the excess in the body will be excreted in the urine.

Discussion

Folic acid or vitamin B9 is a water-soluble vitamin that is essential for carbon metabolism. It plays roles in various cellular reactions such as DNA synthesis, repair, and methylation, thus supporting cell division.[4,10] Folic acid can be found in various food sources, such as nuts, spinach, asparagus, broccoli, green vegetables, and avocado. Folic acid cannot be synthesized in the body and depends entirely on intake from diet or supplementation.[4]

Folic acid also plays a role in the metabolism of homocysteine to methionine. Folic acid deficiency will result in increased levels of homocysteine in the blood and has been linked to metabolic syndrome. Levels of more than 11 µmol/l will increase the risk of cardiovascular disease. Hyperhomocysteinemia will result in impaired endothelial function, increased vascular lesions, and increased platelet adhesiveness.[10] This condition is associated with increased gene expression of proinflammatory cytokines, one of which is CRP, which is produced in the liver.[8,9]

C-reactive protein (CRP) has been shown to be prognostic of the incidence of various diseases in the metabolic syndrome population such as myocardial infarction, stroke, and type 2 DM.[5,8] C-reactive protein levels >3 mg/l are associated with a 1.7 times increased risk of cardiovascular disease in the metabolic syndrome.[5] It is said to has a higher predictive value compared to LDL cholesterol levels.[8] It is has also been shown to impair insulin signaling through the regulation of spleen tyrosine kinase (Syk) on small G-protein pA, jun N-terminal kinase (JNK) mitogen-activated protein kinase (MAPK), insulin receptor substrate-1 (IRS-1), and endothelial nitric oxide synthase (eNOS) in vascular endothelial cells. C-reactive protein has also been shown to contributes to atherothrombosis though endothelial cell activation and dysfunction in vitro as well as in vivo. Lowering the levels of CRP would reduce or prevent these adverse effects and hence reduce the incidence of cardiovascular diseases.[10,11]

Administration of folic acid can reduce CRP levels in metabolic syndrome. Based on the literature search, two articles were found that met the eligibility criteria, namely one systematic review and one randomized controlled trial (RCT). In a systematic review conducted by Jiang et al.,[8] in 2022, it was found that administration of folic acid with varying doses and duration (0.15 mg/day for 12 weeks to 10 mg/day for 2 weeks) significantly reduced CRP levels in metabolic syndrome (WMD= -0.94 95% CI -1.56, -0.32; p=0.00).[8] This supports the idea that administration of folic acid can reduce proinflammatory cytokines. The advantage of this article is that it includes RCTs that use a crossover design. However, there is a weakness, namely that it still includes RCTs with high bias (3.5%).

In the RCT conducted by Schneider et al.,[9] in 2011, each subject was given 5 mg folic acid per day or placebo each for 4 weeks with a wash-out phase between the second phase of the study for 4 weeks, and it was found that administration of folic acid had no effect to decrease CRP levels. According to this RCT, the mean difference of CRP in metabolic syndrome group is smaller than in non-metabolic syndrome group, and this result was not statistically significant.[9] The weakness of this article is that homocysteine levels were not checked, where its level can decrease with folic acid administration by various factors such as dose, absorption, and duration of supplementation. However, the strength of this

article is the method used a crossover design with a 4-week supplementation phase and a 4-week wash-out phase.

Based on these two articles, the effect of folic acid administration on CRP levels in patients with metabolic syndrome is still inconclusive. However, folic acid has the potential to reduce CRP levels, therefore further research is needed. The supplementation dose that can be given is 0.15 mg (150 μg) to 1 mg per day for a minimum of 8 weeks together with the use of statin as an anti-inflammatory agent[12] The upper limit of tolerable intake from supplementation is 1 mg, and acute side effects can occur at a dose of 15 mg (15 times the upper limit of tolerable intake).[13] It is recommended that if facilities are available, serum folic acid levels should be checked prior to supplementation.

Conclusion

Folic acid supplementation can potentially reduce CRP levels in patients with metabolic syndrome and grade 2 obesity. In patients in this case, folic acid supplementation can be given to support in reducing the patient's inflammatory condition.

Conflict of interest

The authors declare there is no conflict of interest regarding this article.

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