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Letter to the Editor

Folic Acid Supplementation for Autoimmune Rheumatic Diseases—Approaches and Opportunities for Research

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Abstract: Introduction: Folate, in its supplemental form as folic acid, plays a crucial role in cellular metabolism, DNA synthesis, and cell division. Folate deficiency can lead to elevated homocysteine (HHcy) levels, which contribute to endothelial dysfunction, atherosclerosis, and cardiovascular disease (CVD). Since CVD is a leading cause of mortality in patients with autoimmune rheumatic diseases (ARDs), investigating folate's potential role in modulating disease progression and inflammatory processes is of clinical relevance. **Objective**: To review the current evidence on the impact of folate supplementation in patients with ARDs. **Methods**: A comprehensive literature search was conducted in PubMed, SciELO, and LILACS databases from 1965 to May 2023, using MeSH terms related to folic acid, folate, and various ARDs. The reference lists of selected articles were also screened to identify additional relevant studies. **Results**: Among all retrieved articles, only one randomized controlled trial met the inclusion criteria. The study included 26 patients, primarily women, with autoimmune hand osteoarthritis (AHO). Participants received either folate alone (6400 mg), folate plus cobalamin (6400 mg + 20 mcg), or a lactose placebo for two months. The combination of folate and cobalamin significantly improved handgrip strength compared with the other groups, achieving outcomes similar to nonsteroidal anti-inflammatory drug (NSAID) therapy but with fewer tender joints and no reported side effects. **Conclusion**: Current evidence on folate supplementation in ARDs remains extremely limited. The available trial suggests potential benefits of folate, particularly when combined with cobalamin, in symptom management for AHO. Given its low cost and favorable safety profile, further randomized, double-blind, placebo-controlled studies are warranted to investigate the efficacy of folate in managing pain and slowing disease progression in ARDs.

Keywords: autoimmune rheumatic diseases; rheumatoid arthritis; folic acid; folate; inflammation

Dear Editor in Chief

Folate, or folic acid in its supplemental form, is an essential cofactor in cellular metabolism, DNA synthesis, and cell division. In its bioactive forms, folate enables the enzymatic transfer of single-carbon moieties in metabolic pathways that support cellular functions, including the synthesis of nucleic acids, amino acids, catecholamines, lipids, and proteins, as well as antioxidant regeneration and epigenetic regulation [1]. According to the European Food Safety Authority (EFSA), the current average requirement (AR) for folate in the diet of healthy adults is 250 µg Dietary Folate Equivalents (DFE)/day, with a Population Reference Intake (PRI) of 330

μg DFE/day [2]. DFE is used to estimate AR because folic acid from supplements and fortified foods is more bioavailable than naturally occurring dietary folate [3]. ARs for children, pregnant women, and lactating women differ from the general adult population and are based on studies indicating the maintenance of serum and erythrocyte folate concentrations [4,5], which should remain ≥10 nmol/L and ≥340 nmol/L, respectively, for optimal function [6].

Folate supplementation below the upper limit (UL) of 1 mg/day has not been associated with adverse side effects [5], and intolerance or hypersensitivity reactions are rare [7,8]. For children, UL values vary from 800 μg/day (ages 15–17 years) to 200 μg/day (ages 1–3 years) [2,4,6]. These limits were established with respect to cobalamin (vitamin B12) deficiency, since folate can mask this deficiency, potentially resulting in irreversible neurological damage [9].

Hallmarks of folate deficiency include macrocytic megaloblastic anemia and neural tube defects in the developing fetus of mothers with insufficient folate levels [9]. Low folate concentrations increase homocysteine (Hcy) levels by reducing methionine synthase activity [10]. Elevated Hcy impairs protein synthesis by reducing the bioavailability of methionine, an essential amino acid, and cysteine, a non-essential amino acid derived from methionine [10,11]. Hyperhomocysteinemia (HHcy) is defined as plasma Hcy levels ≥12 μmol/L in males and ≥10 μmol/L in females [12–14]. HHcy has been linked to endothelial dysfunction (ED) and atherosclerosis [15–18], reduced nitric oxide (NO) synthesis [19,20], increased monocyte recruitment [21,22], enhanced thromboxane synthesis [23], and the development of a prothrombotic and proinflammatory vascular environment [24].

HHcy has also been associated with rheumatic diseases (RD) [22,24]. Mechanisms are believed to involve chronic inflammation depleting folate, with the resulting HHcy contributing to cardiovascular disease (CVD). CVD is the leading cause of mortality in patients with rheumatoid arthritis (RA), who face approximately a twofold increased risk compared with the general population [25–27]. HHcy likely accelerates atherosclerosis in RD patients by reducing NO synthesis, impairing enzymatic degradation of asymmetric dimethylarginine, promoting homocysteinylation-induced oxidative stress, activating the humoral immune response, and enhancing IL-6 and IL-8 production in synoviocytes, in addition to the other mechanisms linking HHcy to ED [28].

Given the strong evidence connecting HHcy with atherosclerosis and RD, further investigation into whether folate supplementation can mitigate or alter autoimmune rheumatic disease (ARD) progression is warranted. Folic acid supplementation has been successfully used in the management of hematological and neuropsychiatric conditions caused by folate deficiency, including macrocytic megaloblastic anemia [29]. Nonetheless, evidence specifically linking ARDs to folate supplementation remains very limited, despite arguments supporting its potential anti-atherosclerotic and anti-inflammatory effects [30]. In the present study, we report the findings of a literature review on folate supplementation and ARDs.

A systematic search of PubMed, SciELO (Scientific Electronic Library Online), EMBASE, Cochrane, and LILACS (Latin American and Caribbean Health Sciences Literature) was conducted without language restrictions, covering the period from 1965 to May 2023. The following MeSH terms were used: “folic acid” OR “folate” AND “rheumatic” OR “rheumatologic” OR “systemic lupus erythematosus” OR “lupus” OR “fibromyalgia” OR “rheumatoid arthritis” OR “spondyloarthritis” OR “Sjögren’s syndrome” OR “myositis” OR “systemic sclerosis” OR “vasculitis” OR “Takayasu disease” OR “Wegener’s disease” OR “granulomatosis with polyangiitis” OR “Kawasaki disease” OR “polyarteritis nodosa” OR “livedoid vasculitis” OR “Churg-Strauss” OR “eosinophilic granulomatosis with polyangiitis” OR “osteoarthritis” OR “gout”. Reference lists of the selected articles were also screened for additional relevant studies. The inclusion criteria were original studies directly assessing folate supplementation in ARDs, regardless of language or year of publication. And the exclusion criteria: non-original articles (e.g., editorials, letters), narrative reviews, isolated case reports, studies not related to ARDs, and studies evaluating multivitamin supplementation without distinguishing the role of folate. Our search strategy initially encompassed both randomized clinical trials and observational studies.

After reviewing titles and abstracts, only one study met the inclusion criteria. In a randomized controlled trial, Flynn and colleagues [31] evaluated folate supplementation in 26 patients, 23 of whom were women, with autoimmune hand osteoarthritis (AHO). Patients received either folate alone (6400 mg), folate plus cobalamin (6400 mg + 20 mcg), or a lactose placebo for two months. At the end of the study, patients in the folate plus cobalamin group had greater handgrip strength compared with the other groups, with outcomes comparable to those of nonsteroidal anti-inflammatory drug (NSAID) users. However, the number of tender joints was significantly higher in NSAID users than in the folate plus cobalamin group. No adverse effects were reported (see Table 1).

Table 1. Characteristics of the randomized controlled trial of folate supplementation in autoimmune hand osteoarthritis (Flynn et al., 1994) [31].

Study (year)	Population	Intervention	Comparator	Duration	Outcomes	Key Findings	Limitations
Flynn et al., 1994 [31]	26 patients (23 women) with autoimmune hand osteoarthritis	Folate 6400 mg/day OR folate 6400 mg + cobalamin 20 µg/day	Placebo (lactose)	2 months	Handgrip strength, tender joint count, comparison with NSAID therapy	Folate + cobalamin improved handgrip strength, similar to NSAID outcomes; fewer tender joints vs. NSAID; no adverse effects reported	Very small sample size; short follow-up; outcomes limited to symptomatic measures, not comprehensive disease activity indices

Some critics to the study are however needed: (i) the trial has very small sample size (n = 26) and short follow-up (two months) limiting both statistical power and the ability to assess durability of effect, long-term safety, and clinically meaningful changes over time; (ii) In the only available trial, outcomes such as handgrip strength and tender joint counts were evaluated; however, these measures are symptomatic proxies that do not fully reflect overall disease activity or inflammatory burden, underscoring the need for future studies to incorporate validated composite indices, functional assessments, and biomarkers.

Although evidence from rheumatoid arthritis consistently shows that folate or folinic acid reduces gastrointestinal and hepatic toxicity associated with methotrexate without impairing its therapeutic efficacy, this body of research addresses only co-therapy and not folate as an independent intervention [32]. In parallel, studies on cardiovascular prevention demonstrate that folate supplementation lowers homocysteine levels and may improve endothelial function, although findings on major cardiovascular outcomes remain inconclusive and derive mainly from non-ARD populations [33]. Together, these observations highlight a critical gap in the literature: the absence of well-designed trials evaluating folate supplementation per se in autoimmune rheumatic diseases. This gap underscores the need for adequately powered, long-term randomized studies incorporating validated disease activity indices and cardiovascular endpoints.

Future research should include larger and more representative cohorts of different autoimmune rheumatic diseases, employing randomized, double-blind, placebo-controlled designs. In addition to clinical outcomes such as pain, disease activity, and quality of life, trials should also incorporate cardiovascular endpoints, given the established association between hyperhomocysteinemia, ARDs, and cardiovascular risk. Moreover, the potential synergistic effects of folate combined with cobalamin warrant further investigation.

In conclusion, our review identified only one study investigating folate in AHO, with promising results. Although the available evidence is extremely limited, it suggests a potential role for folate, particularly when combined with cobalamin, in the management of AHO. Given its low cost and favorable safety profile, further research is warranted to evaluate the efficacy of folate in AHO and other ARDs. Future randomized, double-blind, placebo-controlled, crossover trials with appropriate washout periods, comparing folate and NSAID therapy both in combination and separately, will be essential to clarify the role of folate in pain management and disease progression in ARDs.

Author Contributions

J.F.d.C.: conceptualization, methodology, data curation, writing—original draft preparation; visualization, investigation; supervision. T.L.M.: data curation, writing—original draft preparation; visualization, investigation; reviewing and editing; A.A.B.: conceptualization, methodology, data curation, writing—original draft preparation; visualization, investigation; writing—reviewing and editing. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

No ethical issues have been associated with this study.

Informed Consent Statement

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Data Availability Statement

This study did not generate any new datasets. All information analyzed is already included within the published article, and no additional data are available.

Conflicts of Interest

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this letter

Use of AI and AI-Assisted Technologies

During the preparation of this work, the authors used ChatGPT to improve the English language and refine the clarity of the text in this review article. No part of the analysis or interpretation was generated by AI. After using this tool, the authors carefully reviewed and edited all content and take full responsibility for the final version of the manuscript.

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