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Meta-analyses

Homocysteine-lowering therapy with folic acid is effective in cardiovascular disease prevention in patients with kidney disease: A meta-analysis of randomized controlled trials

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SUMMARY

Background & aims: The efficacy of homocysteine-lowering therapy with folic acid to lower homocysteine levels in an effort to reduce cardiovascular disease (CVD) risk in patients with kidney disease remains inconclusive. We conducted a meta-analysis of relevant randomized trials to further examine this issue.
Methods: This meta-analysis included 8234 patients with kidney disease from nine qualified randomized trials using folic acid therapy, and with CVD reported as one of the endpoints. Relative risk (RR) was used to measure the effect of folic acid supplementation on risk of CVD using a random effects model.
Results: When pooling the nine randomized trials, folic acid therapy reduced the risk of CVD by 10% (RR = 0.90; 95% CI:0.81–1.00, $P = 0.046$). A greater beneficial effect was observed among those trials without a history of grain fortification with folic acid (0.82; 0.70–0.96, $P = 0.01$), with lower percent baseline diabetes (<30% (median), 0.80; 0.65–0.99, $P = 0.04$), and in patients with end-stage renal disease (ESRD) or advanced chronic kidney disease (ACKD) (0.85; 0.77–0.94, $P = 0.002$). Furthermore, a meta-regression analysis suggested a positive dose-response relationship between percent baseline diabetes and log-RR for CVD risk associated with folic acid supplementation ($P = 0.007$). Most importantly, even the inclusion of three subgroup results did not substantially affect the results ($n = 11032$, RR: 0.93; 95% CI:0.87–0.99, $P = 0.03$).
Conclusions: Our meta-analysis indicates that folic acid supplementation may be effective for CVD prevention in patients with kidney disease, particularly in trials among patients without a history of grain fortification with folic acid, with lower percent baseline diabetes, and in patients with ESRD or ACKD.

1. Introduction

Our previous meta-analysis indicated that homocysteine-lowering therapy with folic acid can reduce cardiovascular disease (CVD) risk in patients with end-stage renal disease (ESRD) or advanced chronic kidney disease (ACKD) by 15% (RR: 0.85; 95CI:0.76–0.96, $P = 0.009$). A greater beneficial effect was observed among those trials with no or partial folic acid fortification (RR: 0.80; 95% CI: 0.65–0.99; $P = 0.04$).[1]

However, in light of the growing number of published trials,[2,3] meta-analyses[4] and continuing controversy in the field, a comprehensive meta-analysis of all the available data is warranted to further examine whether homocysteine-lowering therapy with folic acid has a beneficial effect on CVD risk in patients with kidney disease. We also identified the impact of subject characteristics and treatment characteristics on the effect of folic acid on CVD.

2. Materials and methods

2.1. Search strategy and selection criteria

This report followed the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines. We used a similar search strategy and selection criteria as previously reported.[1]

Abbreviations: ACKD, Advanced chronic kidney diseases; CVD, cardiovascular disease; ESRD, End stage renal disease.

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To select pertinent studies, we performed a comprehensive and independent literature search of the Medline database from January1966 to July 2012, with the MESH terms "cardiovascular disease", "cerebrovascular accident", "coronary disease", "coronary thrombosis", "myocardial ischemia", "coronary stenosis", "coronary restenosis", "cerebrovascular accident", "cerebrovascular disease", "stroke" and "folic acid", "folate", "multivitamin", "chronic kidney disease", "end-stage renal disease", "advanced chronic kidney disease", and "dialysis". Manual searches of bibliographies of all relevant trials and review articles also were conducted. The search was restricted to human studies and clinical trials. There were no language restrictions. A team of experts in the relevant disciplines was assembled.

A standard protocol for study selection and data abstraction was developed by our multidisciplinary team with expertise in clinical medicine, epidemiology, clinical trials, and biostatistics. Studies were eligible for inclusion if: (1) the study was a randomized controlled trial; (2) the study was conducted in subjects with kidney disease; (3) the number of cardiovascular events that occurred during the study were reported by intervention and control groups; and (4) the intervention consisted of folic acid therapy (with or without additional B vitamins).

2.2. Data collection

Of the 54 studies potentially eligible, each of the abstracts was reviewed independently by two investigators to determine if it met eligibility criteria for inclusion. All data from eligible trials were independently abstracted in duplicate by two independent investigators using the standard protocol. Discrepancies were resolved by discussion with the third investigator and the multidisciplinary team who developed the protocol.

The following data were extracted: first author's name, year of publication, study design, baseline characteristics (age, sex, and baseline comorbidities), intervention regimen, treatment duration, baseline percent use of antiplatelet agents, and baseline percent use of lipid-lowering drugs.

Studies were assessed for quality of randomization, blinding, reporting of withdrawals, generation of random numbers, and concealment of allocation. Trials scored one point for each area addressed, with a possible score of between 0 and 5 (highest level of quality).[5]

2.3. Statistical analysis

Relative risk (RR) with a 95% confidence interval (95% CI) was used to measure the effect of folic acid supplementation on CVD risk. Heterogeneity between studies was assessed by Cochran's Q test with a significance level set at 0.10. The I^2 statistics was also examined, and we considered I^2 >50% to indicate relevant heterogeneity. Since it is unlikely that all of the heterogeneity in the results will be due to the treatment itself, summary estimates of RR and 95% CIs were obtained by using random-effect (DerSimonian and Laird) models. Previously defined subgroup analyses and meta-regression analyses were performed to explore the influence of study characteristics on effects. For the continuous variables, strata were defined based on above or below the median values. The meta-regression was performed with the relevant factor specified as a random effect (mixed model). Estimation of the residual between-trial variance was based on a restricted maximum likelihood method. The potential for publication bias was examined using a funnel plot and Egger regression test. We also conducted a sensitivity analysis by removing each individual trial from the meta-analysis. All of the analyses were done using R software, version 2.13.0 (http://www.R-project.org/).

2.4. Role of the funding source

There was no funding source for this study. All of the authors have had full access to the data used for this meta-analysis, and have assumed final responsibility for the submission of this manuscript.

3. Results

Of the 54 studies, 45 were excluded for not being randomized trials or for no CVD outcomes. Our final analysis included 9 randomized controlled trials[2,3,6–12] using folic acid therapy and with CVD reported as one of the endpoints, to comprise a total of 8234 individuals. The baseline characteristics of the study participants and design characteristics of these trials are presented in Tables 1 and 2.

The quality of these nine trials ranged from 3 to 5 (maximum score), and they were all randomized, double-blind, and controlled, except for two,[6,7] which were randomized, open-labeled trials.

When pooling the nine randomized trials (Fig. 1), folic acid therapy reduced the risk of CVD by 10% (RR = 0.90; 95% CI: 0.81–1.00, $P = 0.046$). The estimate from a fixed-effects model (RR = 0.91; 95% CI: 0.84–0.99, $P = 0.027$, Fig. 1) yielded a similar result.

In the stratified analysis, a greater beneficial effect was observed among those trials of patients without a history of grain fortification with folic acid[6–10] (0.82; 0.70–0.96, $P = 0.01$), with higher baseline homocysteine levels (≥25 μmol/L (median), 0.87; 0.76–1.00, $P = 0.049$), with higher percent baseline current smoker (≥15% (median), 0.83; 0.73–0.95, $P = 0.005$), with lower percent baseline diabetes (<30% (median), 0.80; 0.65–0.99, $P = 0.04$), and in patients with ESRD or ACKD[6–12] (0.85; 0.77–0.94, $P = 0.002$); in the corresponding comparison group the estimated RRs were attenuated and insignificant. Homocysteine reduction (<30% vs. ≥30%), baseline total cholesterol levels (<4.8 vs. ≥4.8 mmol/L), and intervention regimen (folic acid alone vs. folic acid with vitamin B6 and B12) did not significantly affect the effect of folic acid therapy (Table 3, Fig. 1).

Furthermore, meta-regression analyses suggested a significant positive dose-response trend between percent baseline diabetes (9 trials, regression coefficient = 0.0080; 95% CI: 0.0022, 0.0139; $P = 0.007$) and log-RR for CVD associated with folic acid supplementation (Fig. 2). However, percent baseline current smoker (7 trials, regression coefficient = −0.0042; 95% CI: −0.0092, 0.0009; $P = 0.104$), baseline total cholesterol levels (9 trials, regression coefficient = −0.1008; 95% CI: −0.6344, 0.4328; $P = 0.711$), baseline homocysteine levels (9 trials, regression coefficient = −0.0094; 95% CI: −0.0220, 0.0032; $P = 0.145$), and homocysteine reduction (9 trials, regression coefficient = −0.0042; 95% CI: −0.0095, 0.0011; $P = 0.121$) did not significantly correlate with the effect size.

Furthermore, excluding the two trials[6,7] that were included in our previous meta-analysis[1] but not included in the analysis by Jardine et al.,[4] did not materially alter the results ($n = 8067$, 0.92; 0.84–1.00, $P = 0.05$). Most importantly, even the inclusion of three subgroup results[13–15] did not substantially affect the results ($n = 11032$, 0.93; 0.87–0.99, $P = 0.03$) [Supplementary Figure]. Visual inspection of the funnel plot did not clearly indicate presence of publication bias, and a statistical analysis of funnel plots also did not suggest publication bias (Egger test, $P = 0.99$). Significant heterogeneity ($P \leq 0.10$ and $I^2 \geq 50\%$) are presented in Table 3, Fig. 1 and the Supplementary Figure. Sensitivity analyses showed that the RR and 95% CI did not alter substantially after removing any one trial (data not shown).

4. Discussion

Jardine et al.[4] concluded that folic acid based homocysteine-lowering does not reduce cardiovascular events in people with kidney disease, and folic acid based regimens should not be used for the prevention of cardiovascular events in people with kidney