Australian Traditional-Medicine Society

ATMS

SUBMISSION: DEPARTMENT OF HEALTH

NTREAP – EVIDENCE FOR TRANCHE ONE

Report prepared by:
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Natural Therapies Review 2019-2020
Department of Health

By email: naturaltherapiesreview@health.gov.au

Submission – Citations for published scientific research studies for consideration in the Natural Therapies Review 2019-20

Thank you for the opportunity to make a submission to the Natural Therapies Review 2019-2020.

The Australian Traditional-Medicine Society (ATMS) is Australia's largest national professional association of natural medicine practitioners. ATMS is a multi-modality association representing around 9,000 accredited practitioners and students throughout Australia. ATMS currently accredits 20 natural medicine modalities.

ATMS promotes and represents accredited practitioners of natural medicine, who are encouraged to pursue the highest ideals of professionalism in their natural medicine practice and education.

ATMS has consistently opposed the process, deliberations and outcomes of the 2015 Review of the Australian Government Rebate on Private Health Insurance for Natural Therapies. We have argued that in the 2015 Review the methodology was flawed and the final Report does not provide a sound basis for Australian public policy.

ATMS supports the process currently underway with the Natural Therapies Review Expert Advisory Panel (NTREAP) 2019-2020. The current call for evidence is for natural medicine therapies identified as tranche 1. Of these therapies ATMS currently accredits:

- naturopathy;
- western herbal medicine; and
- shiatsu

The proposed next call for evidence is for natural medicine therapies identified as tranche 2. Of these therapies ATMS currently accredits:

- aromatherapy;
- Bowen therapy;
- homeopathy;
- kinesiology; and
- reflexology.

Attached is a detailed list of evidence to support both the practice of Naturopathy as well as the tools of trade. Evidence has been provided in the form of abstracts and citations for

Naturopathic Practice and the tools of trade for Naturopaths which include Herbal Medicines and Nutritional Supplements. The evidence covers both Systematic Reviews and Meta Analyses as well as Randomised Controlled Trials.

ATMS will make a further submission for tranche 2 when called to do so.

Yours sincerely

Peter Berryman
ATMS President

ATMS acknowledges the contribution to this submission by:

Sandra Grace
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Naturopathic “Whole Practise”

OVERVIEWS

Myers SP, Vigar V/ The State of the Evidence for Whole-System, Multi-Modality Naturopathic Medicine: A Systematic Scoping Review. J Altern Complement Med. 2019 Feb;25(2):141-168. doi: 10.1089/acm.2018.0340.

Abstract

OBJECTIVE: To summarize the current state of the research evidence for whole-system, multi-modality naturopathic medicine.
DESIGN: A systematic search for research articles from around the world was undertaken using MEDLINE, Embase, CINAHL, AMED, and WHO regional indexes. Naturopathic journals and gray literature were hand searched. No language restrictions were imposed.
INTERVENTIONS: All human research evaluating the effectiveness of naturopathic medicine, where two or more naturopathic modalities are delivered by naturopathic clinicians, were included in the review. Case studies of five or more cases were included.
RESULTS: Thirty-three published studies (n = 9859) met inclusion criteria (11 American; 4 Canadian; 6 German; 7 Indian; 3 Australian; 1 United Kingdom; and 1 Japanese) across a range of mainly chronic clinical conditions. The studies predominantly showed evidence for the efficacy of naturopathic medicine for the conditions and settings in which they were based.
CONCLUSIONS: To date, research in whole-system, multi-modality naturopathic medicine shows that it is effective for treating cardiovascular disease, musculoskeletal pain, type 2 diabetes, polycystic ovary syndrome, depression, anxiety, and a range of complex chronic conditions.

KEYWORDS:

global; naturopathic medicine; naturopathy; pragmatic; systematic review; whole-system

Grace S, Barnes L, Reilly W, Vlass A, de Permentier P. An integrative review of dietetic and naturopathic approaches to functional bowel disorders. Complementary Therapies in Medicine, Dec2018; 41: 67-80. http://dx.doi.org.ezproxy1.library.usyd.edu.au/10.1016/j.ctim.2018.09.004Abs

Abstract

OBJECTIVES: Naturopathy and dietetics have evolved as two separate but parallel professions that use diet to promote optimal health and manage many illnesses and diseases. Given the increasing recognition of the influence of diet on health outcomes, there is increasing demand for the services of both professions. The aim of this research

was to investigate similarities and differences between naturopathic and dietetic approaches to functional bowel disorders (FBDs).
DESIGN: For this integrative review AMED, CINAHL, the Cochrane Database of Systematic Reviews, EMBASE, Medline and PubMed databases were searched for articles that focused on dietetic or naturopathic diagnosis and treatment of food intolerance expressing as a FBD in adults. (Registration: PROSPERO 2016 CRD42016049469).
Results: Of the 55 papers in the final review, 10 discussed complementary medicine approaches to FBDs. Both dietitians and naturopaths used similar holistic approaches to diagnosis and treatment, adjusted diets as a primary treatment approach, and individualised treatment for their patients. The professions differed in their use of vitamin, mineral and herbal supplements and in their willingness to recommend other treatments like osteopathy and acupuncture.
CONCLUSIONS: There is much overlap between dietetic and naturopathic approaches to assessment and treatment of FBDs. Further publications that describe naturopathic treatments for FBDs are needed to confirm these results and to provide opportunities for increased recognition and scrutiny of any distinctively naturopathic approaches. Without doing so, naturopathic practices are likely to remain marginalised and poorly understood. Moreover, the opportunity to fully contribute to the management of lifestyle-related diseases will be missed.

Jin AJ, Chin CJ. Complementary and Alternative Medicine in Chronic Rhinosinusitis: A Systematic Review and Qualitative Analysis. Am J Rhinol Allergy. 2019 Mar;33(2):194-202. doi: 10.1177/1945892418813079. Epub 2018 Nov. 28.

Abstract

BACKGROUND: Complementary and alternative medicine (CAM) is frequently used in the treatment of chronic rhinosinusitis (CRS) in developed countries. With a plethora of CAM therapies available, their effectiveness and safety are poorly understood in the context of CRS.
OBJECTIVES: This article aims to critically appraise the evidence for CAM use in CRS through a systematic review of current literature that investigate the effects of CAM on symptoms and clinical status of adults with CRS.
STUDY DESIGN: Systematic review and qualitative analysis.
REVIEW METHODS: A comprehensive systematic review of the literature was conducted by the authors using 5 databases from inception to July 2017: CINAHL, Cochrane, Embase, PubMed, and SCOPUS. Inclusive medical subject headings and keywords consisted of, but were not limited to, sinusitis and complementary therapies, naturopathy, or traditional Chinese medicine. PRISMA guideline was followed. Using templates by Cochrane Public Health Group and Newcastle-Ottawa Scale, each author extracted data, assessed bias, and computed minimal clinically important difference. Any conflicts were resolved through discussion.
RESULTS: In total, 7 of 7141 articles from 1995 to 2016 were included. Three randomized controlled trials and 4 observational studies were organized into 4 categories of CAM: naturopathy, Chinese medicine, homeopathy, and others. Limited evidence

supported the use of Pimpinella anisum and crenotherapy for CRS. Data available on Chinese medicine, homeopathy, and liposomal therapy in CRS were inconclusive due to inherent flaws in the studies.
CONCLUSION: Overall, there is very limited evidence to support the use of CAM in the treatment of CRS. No significant adverse effects have been found. Given its widespread use, more rigorous data from high-quality research are needed before it can be routinely recommended.
KEYWORDS: Chinese traditional medicine; chronic rhinosinusitis; chronic sinusitis; complementary and alternative medicine; homeopathy; naturopathy; otolaryngology

RANDOMISED CONTROLLED TRIALS

Neuendorf R, Corn J, Hanes D, Bradley R. Impact of Food Immunoglobulin G-Based Elimination Diet on Subsequent Food Immunoglobulin G and Quality of Life in Overweight/Obese Adults. J Altern Complement Med. 2019 Feb;25(2):241-248. doi: 10.1089/acm.2018.0310. Epub 2018 Sep 28.

Abstract

OBJECTIVES: The goal of this study was to assess changes in serum immunoglobulin G (IgG) food antibody titers and quality-of-life measurements following a targeted elimination diet in overweight/obese adults.
METHODS: We performed a randomized control trial. Participants were randomized in a 2:1 ratio to either an intervention group or waitlist group for 3 months. Food IgG testing was performed on all participants. The intervention group was instructed to eliminate up to 10 foods, for which they had high titers of IgG and communicated with health coaches for nutritional counseling for meal planning and adherence. The waitlist group did not receive their IgG testing results or health coaching. Primary outcome was serum IgG titers for foods eliminated during the trial, compared with baseline concentrations. Secondary outcomes were health-related quality of life measured by Patient-Reported Outcomes Measurement Information System (PROMIS-29) and change in participant-identified symptom severity measured by Measure Yourself Medical Outcome Profile. Exploratory outcomes were changes in body weight and waist circumference.
RESULTS: IgG antibody concentrations decreased in 83% of the targeted foods in the treatment group and in 60% of the foods in the waitlist group, but this was not found to be a statistically significant difference. The intervention group reported improvement in sleep during the trial compared with waitlist, which was the only statistically significant finding in the study.
CONCLUSIONS: The findings are consistent with changes in IgG titer measurements following an elimination diet based on IgG testing. Future larger clinical trials are necessary to determine the degree to which these findings are generalizable.
KEYWORDS: IgG test; elimination diet; food sensitivity

Herman PM, Szczurko O, Cooley K, Seely D. A naturopathic approach to the prevention of cardiovascular disease: cost-effectiveness analysis of a

pragmatic multi-worksite randomized clinical trial. J Occup Environ Med. 2014 Feb;56(2):171-6. doi: 10.1097/JOM.0000000000000066.

Abstract

OBJECTIVE: To determine the cost-effectiveness of a worksite-based naturopathic (individualized lifestyle counseling and nutritional medicine) approach to primary prevention of cardiovascular disease (CVD).
METHODS: Economic evaluation alongside a pragmatic, multi-worksite, randomized controlled trial comparing enhanced usual care (EUC; usual care plus biometric screening) to the addition of a naturopathic approach to CVD prevention (NC+EUC).
RESULTS: After 1 year, NC+EUC resulted in a net decrease of 3.3 (confidence interval: 1.7 to 4.8) percentage points in 10-year CVD event risk (number needed to treat = 30). These risk reductions came with average net study-year savings of $1138 in societal costs and $1187 in employer costs. There was no change in quality-adjusted life years across the study year.
CONCLUSIONS: A naturopathic approach to CVD primary prevention significantly reduced CVD risk over usual care plus biometric screening and reduced costs to society and employers in this multi-worksite-based study.
Trial Registration clinicaltrials.gov Identifier: NCT00718796.

Seely D, Szczurko O, Cooley K, Fritz H, Aberdour S, Herrington C, Herman P, Rouchotas P, Lescheid D, Bradley R, Gignac T, Bernhardt B, Zhou Q, Guyatt G. Naturopathic medicine for the prevention of cardiovascular disease: a randomized clinical trial. CMAJ. 2013 Jun 11;185(9):E409-16. doi: 10.1503/cmaj.120567. Epub 2013 Apr 29.

Abstract

BACKGROUND: Although cardiovascular disease may be partially preventable through dietary and lifestyle-based interventions, few individuals at risk receive intensive dietary and lifestyle counselling. We performed a randomized controlled trial to evaluate the effectiveness of naturopathic care in reducing the risk of cardiovascular disease.
METHODS: We performed a multisite randomized controlled trial of enhanced usual care (usual care plus biometric measurement; control) compared with enhanced usual care plus naturopathic care (hereafter called naturopathic care). Postal workers aged 25-65 years in Toronto, Vancouver and Edmonton, Canada, with an increased risk of cardiovascular disease were invited to participate. Participants in both groups received care by their family physicians. Those in the naturopathic group also received individualized care (health promotion counselling, nutritional medicine or dietary supplementation) at 7 preset times in work-site clinics by licensed naturopathic doctors. The body weight, waist circumference, lipid profile, fasting glucose levels and blood pressure of participants in both groups were measured 3 times during a 1-year period. Our primary outcomes were the 10-year risk of having a cardiovascular event (based on the Framingham risk algorithm) and the

prevalence of metabolic syndrome (based on the Adult Treatment Panel III diagnostic criteria).
RESULTS: Of 246 participants randomly assigned to a study group, 207 completed the study. The characteristics of participants in both groups were similar at baseline. Compared with participants in the control group, at 52 weeks those in the naturopathic group had a reduced adjusted 10-year cardiovascular risk (control: 10.81%; naturopathic group: 7.74%; risk reduction -3.07% [95% confidence interval (CI) -4.35% to -1.78%], $p < 0.001$) and a lower adjusted frequency of metabolic syndrome (control group: 48.48%; naturopathic care: 31.58%; risk reduction -16.90% [95% CI -29.55% to -4.25%], $p = 0.002$).
INTERPRETATION: Our findings support the hypothesis that the addition of naturopathic care to enhanced usual care may reduce the risk of cardiovascular disease among those at high risk.
TRIAL REGISTRATION: ClinicalTrials.gov, no. NCT0071879.

Cooley K, Szczurko O, Perri D, Mills EJ, Bernhardt B, Zhou Q, Seely D. Naturopathic care for anxiety: a randomized controlled trialISRCTN78958974. PLoS One. 2009 Aug 31;4(8):E6628. doi: 10.1371/journal.pone.0006628.

Abstract

BACKGROUND: Anxiety is a serious personal health condition and represents a substantial burden to overall quality of life. Additionally anxiety disorders represent a significant cost to the health care system as well as employers through benefits coverage and days missed due to incapacity. This study sought to explore the effectiveness of naturopathic care on anxiety symptoms using a randomized trial.
METHODS: Employees with moderate to severe anxiety of longer than 6 weeks duration were randomized based on age and gender to receive naturopathic care (NC) (n = 41) or standardized psychotherapy intervention (PT) (n = 40) over a period of 12 weeks. Blinding of investigators and participants during randomization and allocation was maintained. Participants in the NC group received dietary counseling, deep breathing relaxation techniques, a standard multi-vitamin, and the herbal medicine, ashwagandha (Withania somnifera) (300 mg b.i.d. standardized to 1.5% with anolides, prepared from root). The PT intervention received psychotherapy, and matched deep breathing relaxation techniques, and placebo. The primary outcome measure was the Beck Anxiety Inventory (BAI) and secondary outcome measures included the Short Form 36 (SF-36), Fatigue Symptom Inventory (FSI), and Measure Yourself Medical Outcomes Profile (MY-MOP) to measure anxiety, mental health, and quality of life respectively. Participants were blinded to the placebo-controlled intervention.
RESULTS: Seventy-five participants (93%) were followed for 8 or more weeks on the trial. Final BAI scores decreased by 56.5% ($p<0.0001$) in the NC group and 30.5% ($p<0.0001$) in the PT group. BAI group scores were significantly decreased in the NC group compared to PT group ($p = 0.003$). Significant differences between groups were also observed in mental health, concentration, fatigue, social functioning, vitality, and overall quality of life with the NC group exhibiting greater clinical benefit. No serious adverse reactions were observed in either group.

RELEVANCE: Many patients seek alternatives and/or complementary care to conventional anxiety treatments. To date, no study has evaluated the potential of a naturopathic treatment protocol to effectively treat anxiety. Knowledge of the efficacy, safety or risk of natural health products, and naturopathic treatments is important for physicians and the public in order to make informed decisions.
INTERPRETATION: Both NC and PT led to significant improvements in patients' anxiety. Group comparison demonstrated a significant decrease in anxiety levels in the NC group over the PT group. Significant improvements in secondary quality of life measures were also observed in the NC group as compared to PT. The whole system of naturopathic care for anxiety needs to be investigated further including a closer examination of the individual components within the context of their additive effect.
TRIAL REGISTRATION: Controlled-Trials.com ISRCTN78958974.

Szczurko O1, Cooley K, Mills EJ, Zhou Q, Perri D, Seely D. Naturopathic treatment of rotator cuff tendinitis among Canadian postal workers: a randomized controlled trial. Arthritis Rheum. 2009 Aug 15;61(8):1037-45. doi: 10.1002/art.24675.

Abstract

OBJECTIVE: To explore the effectiveness of naturopathic care (NC) on rotator cuff tendinitis using a prospective randomized clinical trial design.
METHODS: Canadian postal workers with rotator cuff tendinitis for a duration of >6 weeks were randomized to receive NC (n = 43) or standardized physical exercises (PEs; n = 42) over 12 weeks. Participants in the NC group received dietary counseling, acupuncture, and Phlogenzym (2 tablets 3 times/day). The PE intervention group received passive, active-assisted, and active range of motion exercises and matched placebo. The primary outcome measure was the Shoulder Pain and Disability Index (SPADI), and secondary outcomes were the pain visual analogue scale (VAS), Short Form 36 (SF-36), Measure Yourself Medical Outcomes Profile (MYMOP), and shoulder maximal range of motion. Participants and assessors were blinded to group and placebo allocation.
RESULTS: Seventy-seven participants (87%) completed >or=8 weeks of the trial. Final total SPADI scores decreased by 54.5% ($P < 0.0001$) in the NC group and by 18% ($P = 0.0241$) in the PE group. Between-group differences in changes to SPADI scores showed statistically significant decreases in shoulder pain and disability in the NC group compared with the PE group ($P < 0.0001$). Significant differences between groups were also observed in the pain VAS, MYMOP, SF-36, and shoulder extension, flexion, and abduction, with the NC group showing superiority in each outcome. No serious adverse reactions were observed.
CONCLUSION: NC and PE provided significant improvements, with greater improvement in shoulder function in the NC group compared with the PE group. Statistically significant improvements in quality of life measures were observed in the NC group as compared with the PE group.

Naturopathic “Tools of Trade”

B VITAMINS

OVERVIEWS

Gastrointestinal Disorders

Pan Y, Liu Y, Guo H, Jabir MS, Liu X, Cui W, Li D. Associations between folate and vitamin B12 levels and inflammatory bowel disease: A meta-analysis. Nutrients. 2017 Apr;9(4):382.

Abstract

BACKGROUND: Inflammatory bowel disease (IBD) patients may be at risk of vitamin B12 and folate insufficiencies, as these micronutrients are absorbed in the small intestine, which is affected by IBD. However, a consensus has not been reached on the association between IBD and serum folate and vitamin B12 concentrations.
METHODS: In this study, a comprehensive search of multiple databases was performed to identify studies focused on the association between IBD and serum folate and vitamin B12 concentrations. Studies that compared serum folate and vitamin B12 concentrations between IBD and control patients were selected for inclusion in the meta-analysis.
RESULTS: The main outcome was the mean difference in serum folate and vitamin B12 concentrations between IBD and control patients. Our findings indicated that the average serum folate concentration in IBD patients was significantly lower than that in control patients, whereas the mean serum vitamin B12 concentration did not differ between IBD patients and controls. In addition, the average serum folate concentration in patients with ulcerative colitis (UC) but not Crohn's disease (CD) was significantly lower than that in controls. This meta-analysis identified a significant relationship between low serum folate concentration and IBD.
CONCLUSIONS: Our findings suggest IBD may be linked with folate deficiency, although the results do not indicate causation. Thus, providing supplements of folate and vitamin B12 to IBD patients may improve their nutritional status and prevent other diseases.
KEYWORDS: folate; inflammatory bowel disease; meta-analysis; nutrition; vitamin B12

Cardiometabolic Disease and Risk

Akbari M, Tabrizi R, Lankarani KB, Heydari ST, Karamali M, Kashanian M et al. The effects of folate supplementation on diabetes biomarkers among patients with metabolic diseases: a systematic review and meta-analysis of randomized controlled trials. Horm Metab Res. 2018 Feb;50(2):93-105. doi: 10.1055/s-0043-125148.

Abstract

Although several studies have evaluated the effect of folate supplementation on diabetes biomarkers among patients with metabolic diseases, findings are inconsistent. This review of randomized controlled trials (RCTs) was performed to summarize the evidence on the effects of folate supplementation on diabetes biomarkers among patients with metabolic diseases. Randomized-controlled trials (RCTs) published in PubMed, EMBASE, Web of Science and Cochrane Library databases up to 1 September 2017 were searched. Two review authors independently assessed study eligibility, extracted data, and evaluated risk of bias of included studies. Heterogeneity was measured with a Q-test and with I^2 statistics. Data were pooled by using the fix or random-effect model based on the heterogeneity test results and expressed as standardized mean difference (SMD) with 95% confidence interval (CI). A total of sixteen randomized controlled trials involving 763 participants were included in the final analysis. The current meta-analysis showed folate supplementation among patients with metabolic diseases significantly decreased insulin (SMD -1.28; 95% CI, -1.99, -0.56) and homeostasis model assessment of insulin resistance (HOMA-IR) (SMD -1.28; 95% CI, -1.99, -0.56). However, folate supplementation did not affect fasting plasma glucose (FPG) (SMD -0.30; 95% CI, -0.63, 0.02) and hemoglobin A1C (HbA1c) (SMD -0.29; 95% CI, -0.61, 0.03). The results of this meta-analysis study demonstrated that folate supplementation may result in significant decreases in insulin levels and HOMA-IR score, but does not affect FPG and HbA1c levels among patients with metabolic diseases.

Barber GA, Weller CD, Gibson SJ. Effects and associations of nutrition in patients with venous leg ulcers: a systematic review. Journal of advanced nursing. 2018 Apr;74(4):774-87.

Abstract

AIMS: To identify the associations and effects of nutritional characteristics and interventions on ulcer outcomes in adult patients with venous leg ulcers.
BACKGROUND: Venous leg ulcers are the most prevalent type of lower limb ulcer; however, little evidence exists regarding the relationship between nutritional status and ulcer healing.
DESIGN: A systematic search of English language articles was conducted using the Cochrane Collaboration Handbook for Systematic Reviews of Interventions.
DATA SOURCES: A search of databases Ovid MEDLINE, EMBASE, Cochrane, CINAHL and Scopus was performed for studies published between January 2004 - May 2017.
REVIEW METHODS: Quality of the included studies was assessed using the Cochrane Collaboration's Risk of Bias Assessment tool and the relevant Joanna Briggs Institute quality appraisal checklists.
RESULTS: Twenty studies met the inclusion criteria. All participants had Clinical Aetiology Anatomy Pathophysiology classification C5 (healed) or C6 (active) ulcers. Studies were conducted in a range of clinical settings with relatively small sample sizes. The majority of patients were overweight or obese. Increased body mass index was associated with delayed wound healing. Vitamin D, folic acid and flavonoids were associated with some

beneficial effects on ulcer healing. Dietary intakes of omega-3 fatty acids, vitamin C and zinc were low for some patients.
CONCLUSION: Current evidence suggests that venous leg ulcer patients are more likely to be overweight or obese. However, evidence for weight management improving wound healing is lacking. Micronutrients, including vitamin D and folic acid, may improve wound healing in at-risk patients.

Ding Y, Li Y, Wen A. Effect of niacin on lipids and glucose in patients with type 2 diabetes: a meta-analysis of randomized, controlled clinical trials. Clin Nutr. 2015;(5):838. doi: 10.1016/j.clnu.2014.09.019.

Abstract

BACKGROUND & AIMS: This study aims to conduct a meta-analysis to evaluate the effects of niacin on serum lipids and glucose in patients with type 2 diabetes mellitus (T2DM).
METHODS: A comprehensive literature search in Medline, Scopus, AMED, Cochrane and Clinical trial registry databases was performed to identify randomized controlled trials investigating the effect of niacin on serum HDL cholesterol (HDL-c), LDL cholesterol (LDL-c), triglycerides (TG) and fasting plasma glucose (FPG). Pooled effects were measured by weighted mean difference (WMD) using fixed-effects or random-effects models. Quality assessment, and subgroup, meta-regression and sensitivity analyses were conducted using standard methods. Inter-study heterogeneity was assessed and quantified.
RESULTS: The estimated pooled mean changes (95% confidence interval) with niacin were 0.27 (95% CI: 0.24 to 0.30; P < 0.001) mmol/L for HDL-c, -0.250 (95% CI: -0.47 to -0.03; P < 0.05) mmol/L for LDL-c and -0.39 (95% CI: -0.43 to -0.34; P < 0.001) mmol/L for TG compared with controls. There was a significant heterogeneity for the impact of niacin on LDL-c and FPG. Subgroup analyses revealed a significant increase in FPG 0.085 (95% CI: 0.029 to 0.141; P < 0.05) mmol/L compared with controls in patients with long term treatment. Our analysis also showed the absence of publication bias and any dose-response relations between niacin and effect size.
CONCLUSIONS: Analysis of the results showed that niacin alone or in combination significantly improved lipid abnormalities in patients with TDM, but requires monitoring of glucose in long term treatment.

KEYWORDS: Clinical trial; Meta-analysis; Niacin; Type 2 diabetes

Jayedi A, Zargar MS. Intake of vitamin B6, folate, and vitamin B12 and risk of coronary heart disease: A systematic review and dose-response meta-analysis of prospective cohort studies. Critical reviews in food science and nutrition. 2018 Sep 18:1-1.

Abstract

The objective of this study was to quantify the association of B-vitamins intake with the future risk of coronary heart disease (CHD). A systematic search was performed with the use of PubMed and Scopus from inception to April 30, 2018. Prospective cohort studies

evaluating the association of intake of folate, vitamin B6, and vitamin B12 with risk of CHD in the general population were included. A random-effects meta-analysis was performed. Eleven prospective cohort studies (total $n = 369,746$) with 5133 cases of CHD were included in the analyses. The relative risks were: 0.79 (95%CI: 0.69, 0.89; $I^2 = 67\%$) for a 250 µg/d increment in folate intake; 0.87 (95%CI: 0.78, 0.96; $I^2 = 80\%$) for a 0.5 mg/d increment in vitamin B6 intake; and 0.97 (95%CI: 0.80, 1.14: $I^2 = 67\%$) for a 3 µg/d increment in vitamin B12 intake. The results did not change materially when the analyses were restricted only to dietary vitamins intake. A nonlinear dose-response meta-analysis demonstrated a linear inverse association between folate and vitamin B6 intake and risk of CHD. In conclusion, higher intake of folate and vitamin B6 is associated with a lower risk of CHD in the general population.

KEYWORDS: Coronary heart disease; folic acid; meta-analysis; vitamin B6

Özturan A, Arslan S, Kocaadam B, Elibol E, İmamoğlu İ, Karadağ MG. Effect of inositol and its derivatives on diabetes: a systematic review. Crit Rev Food Sci Nutr. 2019;59(7):1124-1136. doi: 10.1080/10408398.2017.1392926.

Abstract

A growing body of research has investigated the association between inositol and diabetes. The purpose of this review is to report through a systematic way the current scientific evidence relating potential benefits of inositol isomers on diabetes/gestational diabetes. The screening of the studies published last decade was performed in 4 databases (Pubmed-Web of Science-The Cochrane Library-Lilacs). Among the 1640 studies identified in the search, only 26 studies had sufficient data to be included in the systematic review. The available literature suggests that inositol seems to be provide improvements in fasting blood glucose and other biochemical results, which are among the most important parameters in diabetic individuals. Although there are some studies demonstrating that inositol may be effective in prevention and treatment of diabetes/gestational diabetes, conduction of studies with larger sample and longer follow-up duration is required for it to be represented as an effective strategy in management of diabetes.

KEYWORDS: D-chiro-inositol; Diabetes; gestational diabetes; inositol; myo-inositol

Sahebkar A, Reiner Ž, Simental-Mendía LE, Ferretti G, Cicero AFG. Effect of extended-release niacin on plasma lipoprotein(a) levels: a systematic review and meta-analysis of randomized placebo-controlled trials. Metabolism. 2016 Nov 1;65(11):1664–78.

Abstract

AIM: Lipoprotein(a) (Lp(a)) is a proatherogenic and prothrombotic lipoprotein. Our aim was to quantify the extended-release nicotinic acid Lp(a) reducing effect with a meta-analysis of the available randomized clinical trials.
METHODS: A meta-analysis and random-effects meta-regression were performed on data

pooled from 14 randomized placebo-controlled clinical trials published between 1998 and 2015, comprising 17 treatment arms, which included 9013 subjects, with 5362 in the niacin arm.
RESULTS: The impact of ER niacin on plasma Lp(a) concentrations was reported in 17 treatment arms. Meta-analysis suggested a significant reduction of Lp(a) levels following ER niacin treatment (weighted mean difference - WMD: -22.90%, 95% CI: -27.32, -18.48, p<0.001). Results also remained similar when the meta-analysis was repeated with standardized mean difference as summary statistic (WMD: -0.66, 95% CI: -0.82, -0.50, p<0.001). When the studies were categorized according to the administered dose, there was a comparable effect between the subsets of studies with administered doses of <2000mg/day (WMD: -21.85%, 95% CI: -30.61, -13.10, p<0.001) and ≥2000mg/day (WMD: -23.21%, 95% CI: -28.41, -18.01, p<0.001). The results of the random-effects meta-regression did not suggest any significant association between the changes in plasma concentrations of Lp(a) with dose (slope: -0.0001; 95% CI: -0.01, 0.01; p=0.983), treatment duration (slope: -0.40; 95% CI: -0.97, 0.17; p=0.166), and percentage change in plasma HDL-C concentrations (slope: 0.44; 95% CI: -0.48, 1.36; p=0.350).
CONCLUSION: In this meta-analysis of randomized placebo-controlled clinical trials, treatment with nicotinic acid was associated with a significant reduction in Lp(a) levels.
KEYWORDS: Extended release niacin; Lipoprotein(a); Meta-analysis; Systematic review

Tabrizi R, Ostadmohammadi V, Lankarani KB, Peymani P, Akbari M, Kolahdooz F et al. The effects of inositol supplementation on lipid profiles among patients with metabolic diseases: a systematic review and meta-analysis of randomized controlled trials. Lipids Health Dis. 2018 May 24;17(1):123. doi: 10.1186/s12944-018-0779-4.

Abstract

BACKGROUND: Several studies have evaluated the effect of inositol supplementation on lipid profiles among population with metabolic diseases; however, the findings are controversial. This review of randomized controlled trials (RCTs) was performed to summarize the evidence of the effects of inositol supplementation on lipid profiles among population with metabolic diseases.
METHODS: Relevant RCTs studies were searched in Cochrane Library, EMBASE, MEDLINE, and Web of Science until October 2017. Two researchers assessed study eligibility, extracted data, and evaluated risk of bias of included primary studies, independently. To check for the heterogeneity among included studies Q-test and I2 statistics were used. Data were pooled by using the random-effect model and standardized mean difference (SMD) was considered as summary of the effect size.
RESULTS: Overall, 14 RCTs were included into meta-analysis. Pooled results showed that inositol supplementation among patients with metabolic diseases significantly decreased triglycerides (SMD - 1.24; 95% CI, - 1.84, - 0.64; P < 0.001), total- (SMD - 1.09; 95% CI, - 1.83, - 0.55; P < 0.001), and LDL-cholesterol levels (SMD - 1.31; 95% CI, - 2.23, - 0.39; P = 0.005). There was no effect of inositol supplementation on HDL-cholesterol levels (SMD 0.20; 95% CI, - 0.27, 0.67; P = 0.40).

CONCLUSIONS: Inositol supplementation may result in reduction in triglycerides, total- and LDL-cholesterol levels, but did not affect HDL-cholesterol levels among patients with metabolic diseases. Additional prospective studies regarding the effect of inositol supplementation on lipid profiles in patients with metabolic diseases are necessary.
KEYWORDS: Inositol; Lipid profiles; Meta-analysis; Metabolic diseases

Tian T, Yang KQ, Cui JG, Zhou LL, Zhou XL. Folic acid supplementation for stroke prevention in patients with cardiovascular disease. The American journal of the medical sciences. 2017 Oct 1;354(4):379-87.

Abstract

BACKGROUND: Controversy remains regarding the efficacy of folic acid supplementation in reducing the risk of stroke. This study aimed to evaluate the effect of folic acid supplementation on stroke prevention in patients with cardiovascular disease (CVD).
MATERIALS AND METHODS: We searched the PubMed, EMBASE and Cochrane Library databases through October 2016 to identify randomized clinical trials of folic acid supplementation to prevent stroke in patients with CVD. Relative risks (RRs) with 95% CIs were used to examine the association between folic acid supplementation and the risk of stroke with a fixed-effect model. Stratified analyses were performed according to modifiers that may affect the efficacy of folic acid supplementation.
RESULTS: Eleven studies with a total of 65,790 participants were included. Folic acid supplementation was associated with a significant benefit in reducing the risk of stroke in patients with CVD (RR = 0.90; 95% CI: 0.84-0.97; P = 0.005). In the stratified analysis, greater beneficial effects were observed in participants with a decrease in homocysteine concentrations of 25% or greater (RR = 0.85; 95% CI: 0.74-0.97; P = 0.03), those with a daily folate dose of less than 2mg (RR = 0.78; 95% CI: 0.68-0.89; P = 0.01), and populations in regions with no or partly fortified grain (RR = 0.87; 95% CI: 0.81-0.94; P = 0.04).
CONCLUSIONS: Our meta-analysis demonstrated that folic acid supplementation is effective in stroke prevention in patients with CVD.
KEYWORDS: Cardiovascular disease; Folic acid; Homocysteine; Meta-analysis; Stroke

Wang WW, Wang XS, Zhang ZR, He JC, Xie CL. A meta-analysis of folic acid in combination with anti-hypertension drugs in patients with hypertension and hyperhomocysteinemia. Frontiers in pharmacology. 2017 Aug. 31;8:585.

Abstract

Folic acid is generally used to lower homocysteine concentrations and prevent stroke and cardiovascular disease (CVD) at present. However, the efficacy of therapies that lower homocysteine concentrations in reducing the risk of CVD and stroke remains controversial. Our objective was to do a meta-analysis of relevant randomized controlled trials (RCTs) to evaluate the efficacy of folic acid supplementation among patients with hypertension and Hyperhomocysteinemia (HT/HHcy). We included RCTs examining the effects of folic

acid plus antihypertensive therapy compared to antihypertensive alone. Weighted Mean Difference (WMD) and Relative risk (RR) were used as a measure of the effect of folic acid on the outcome measures with a random effect model. Sixty-five studies including 7887 patients met all inclusion criteria. Among them, 49 trials reported significant effect of combination therapy for reducing SBP (systolic Blood Pressure) and DBP (Diastolic Blood Pressure) levels compared with antihypertensive alone (WMD = -7.85, WMD = -6.77, respectively). Meanwhile, folic acid supplementation apparently reduced the level of total homocysteine (WMD = 5.5). In addition, folic acid supplementation obviously reduced the risk of cardiovascular and cerebrovascular events (CVCE) by 12.9% compared with control groups. In terms of the stratified analyses, a bigger beneficial effect was seen in those RCTs with treatment duration of more than 12 weeks, a decrease in the concentration of total homocysteine of more than 25%, with folic acid fortification. Our findings indicated that folic acid supplementation was effective in the primary prevention of CVCE among HT/HHcy patients, as well as reducing the blood pressure and total homocysteine levels.

KEYWORDS: Antihypertensive; enalapril; folic acid; hyperhomocysteinemia; hypertension; meta-analysis

Zhao JV, Schooling CM, Zhao JX. The effects of folate supplementation on glucose metabolism and risk of type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. Ann Epidemiol. 2018 Apr;28(4):249-257.e1. doi: 10.1016/j.annepidem.2018.02.001.

Abstract

PURPOSE: Observationally, homocysteine is associated with higher risk of diabetes. Folate, which reduces homocysteine, is promising for the prevention and treatment of diabetes. Previous meta-analysis of three trials suggested folate might lower hemoglobin A1c (HbA1c).
METHODS: An updated systematic review and meta-analysis of placebo-controlled randomized trials was conducted. We searched PubMed using ("folate" or "folic acid") and trial and ("glucose" or "diabetes" or "insulin" or "hemoglobin A1c" or "HbA1c") in any field until February 3, 2017. We also conducted a bibliographic search of selected studies and relevant reviews. Relative risk of diabetes and mean differences in indicators of glucose metabolism between folate and placebo were summarized in a meta-analysis using inverse variance weighting with random effects. Heterogeneity, publication bias, and risk of bias were also assessed.
RESULTS: Eighteen trials of 21,081 people with/without diabetes were identified. Folate decreased fasting glucose (-0.15 mmol/L, 95% confidence interval [CI] -0.29 to -0.01), homeostatic model assessment-insulin resistance (-0.83, 95% CI -1.31 to -0.34), and insulin (-1.94 μIU/mL, 95% CI -3.28 to -0.61) but had no clear effect on diabetes or HbA1c.
CONCLUSIONS: Our study suggests a potential benefit of folate on insulin resistance and glycemic control; the latter requires examination in more high-quality trials.
KEYWORDS: Diabetes; Folate; Insulin resistance; Meta-analysis

Fertility and Reproductive Disorders

Irani M, Amirian M, Sadeghi R, Le Lez J, Roudsari RL. The effect of folate and folate plus zinc supplementation on endocrine parameters and sperm characteristics in sub-fertile men: a systematic review and meta-analysis. Urology journal. 2017 Aug 29;14(5):4069-78.

Abstract

PURPOSE: To evaluate the effect of folate and folate plus zinc supplementation on endocrine parameters and sperm characteristics in sub fertile men.
MATERIALS AND METHODS: We conducted a systematic review and meta-analysis. Electronic databases of Medline, Scopus , Google scholar and Persian databases (SID, Iran medex, Magiran, Medlib, Iran doc) were searched from 1966 to December 2016 using a set of relevant keywords including "folate or folic acid AND (infertility, infertile, sterility)".All available randomized controlled trials (RCTs), conducted on a sample of sub fertile men with semen analyses, who took oral folic acid or folate plus zinc, were included. Data collected included endocrine parameters and sperm characteristics. Statistical analyses were done by Comprehensive Meta-analysis Version 2.
RESULTS: In total, seven studies were included. Six studies had sufficient data for meta-analysis. "Sperm concentration was statistically higher in men supplemented with folate than with placebo (P < .001)". However, folate supplementation alone did not seem to be more effective than the placebo on the morphology (P = .056) and motility of the sperms (P = .652). Folate plus zinc supplementation did not show any statistically different effect on serum testosterone (P = .86), inhibin B (P = .84), FSH (P = .054), and sperm motility (P = .169) as compared to the placebo. Yet, folate plus zinc showed statistically higher effect on the sperm concentration (P < .001), morphology (P < .001), and serum folate level (P < .001) as compared to placebo.
CONCLUSION: Folate plus zinc supplementation has a positive effect on sperm characteristics in sub fertile men. However, these results should be interpreted with caution due to the important heterogeneity of the studies included in this meta-analysis. Further trials are still needed to confirm the current findings.

Laganà AS, Vitagliano A, Noventa M, Ambrosini G, D'Anna R. Myo-inositol supplementation reduces the amount of gonadotropins and length of ovarian stimulation in women undergoing IVF: a systematic review and meta-analysis of randomized controlled trials. Arch Gynecol Obstet. 2018 Oct;298(4):675-684. doi: 10.1007/s00404-018-4861-y.

Abstract

PURPOSE: To evaluate whether oral myo-inositol supplementation (MI) is able to reduce the amount of gonadotropins (GA) and the length of controlled ovarian hyperstimulation (SL) in both Polycystic Ovarian Syndrome (PCOS) and non-PCOS women undergoing in vitro fertilization (IVF).
METHODS: We performed a systematic review (PROSPERO ID: CRD42017069439) of randomized controlled trials (RCTs). We searched articles published in English between

January 1985 to August 2017, using the combination of the Medical Subject Headings "Inositol" with "Ovulation Induction", "follicle-stimulating hormone, human, with HCG C-terminal peptide", "Reproductive Techniques, Assisted", and "Fertilization in Vitro". We collected data about GA and SL comparing MI to no treatment or D-Chiro-Inositol (DCI) supplementation (controls). A subgroup analysis was performed to evaluate selected outcomes in PCOS and non-PCOS women.
RESULTS: We included 8 studies embedding 812 participants. We found a reduction in GA ($p < 0.00001$) and SL ($p = 0.0007$) in patients receiving MI with respect to controls. MI was effective in both PCOS ($p < 0.00001$) and non-PCOS women ($p = 0.02$) in reducing GA; conversely, MI supplementation decreased the SL only in PCOS women ($p < 0.00001$).
CONCLUSION: During IVF, MI is effective in both PCOS and non-PCOS women in saving gonadotropins, but reduces efficiently SL only in PCOS women.
KEYWORDS: Controlled ovarian hyperstimulation; In vitro fertilization; Myo-inositol; Recombinant follicle-stimulating hormone

Pundir J, Psaroudakis D, Savnur P, Bhide P, Sabatini L, Teede H et al. Inositol treatment of anovulation in women with polycystic ovary syndrome: a meta-analysis of randomised trials. BJOG. 2018 Feb;125(3):299-308. doi: 10.1111/1471-0528.14754.

Abstract

Polycystic ovary syndrome is a common cause of anovulation and infertility, and a risk factor for development of metabolic syndrome and endometrial cancer. Systematic review and meta-analysis of randomised controlled trials (RCT) that evaluated the effects of inositol as an ovulation induction agent. We searched MEDLINE, EMBASE, Cochrane and ISI conference proceedings, Register and Meta-register for RCT and WHO trials' search portal. We included studies that compared inositol with placebo or other ovulation induction agents. Quality of studies was assessed for risk of bias. Results were pooled using random effects meta-analysis and findings were reported as relative risk or standardised mean differences. We included ten randomised trials. A total of 362 women were on inositol (257 on myo-inositol; 105 on di-chiro-inositol), 179 were on placebo and 60 were on metformin. Inositol was associated with significantly improved ovulation rate (RR 2.3; 95% CI 1.1-4.7; $I^2 = 75\%$) and increased frequency of menstrual cycles (RR 6.8; 95% CI 2.8-16.6; $I^2 = 0\%$) compared with placebo. One study reported on clinical pregnancy rate with inositol compared with placebo (RR 3.3; 95% CI 0.4-27.1), and one study compared with metformin (RR 1.5; 95% CI 0.7-3.1). No studies evaluated live birth and miscarriage rates. Inositol appears to regulate menstrual cycles, improve ovulation and induce metabolic changes in polycystic ovary syndrome; however, evidence is lacking for pregnancy, miscarriage or live birth. A further, well-designed multicentre trial to address this issue to provide robust evidence of benefit is warranted.

Unfer V, Facchinetti F, Orrù B, Giordani B, Nestler J. Myo-inositol effects in women with PCOS: a meta-analysis of randomized controlled trials. Endocrine connections. 2017 Nov 1;6(8):647-58.

Abstract

Myo-inositol (MI) supplementation in women with polycystic ovary syndrome (PCOS) has been evaluated over the last years. Many hormonal and reproductive impairments associated with this disorder seem relieved by the supplement. The objective of the meta-analysis was to assess the effects of MI alone or combined with d-chiro-inositol (DCI) on the endocrine and metabolic abnormalities of women with PCOS. Literature was retrieved from selected databases, MEDLINE, EMBASE, PubMed and Research Gate (up to November 2016). Only randomized controlled trials (RCTs) investigating the effects of MI alone or combined with DCI were reviewed. Nine RCTs involving 247 cases and 249 controls were included. Significant decreases in fasting insulin (SMD = -1.021 μU/mL, 95% CI: -1.791 to -0.251, *P* = 0.009) and homeostasis model assessment (HOMA) index (SMD = -0.585, 95% CI: -1.145 to -0.025, *P* = 0.041) were identified after MI supplementation. The trial sequential analysis of insulin meta-analysis illustrates that the cumulative *z*-curve crossed the monitoring boundary, providing firm evidence of the intervention effect. A slight trend toward a reduction of testosterone concentration by MI with respect to controls was found (SMD = -0.49, 95% CI: -1.072 to 0.092, *P* = 0.099), whereas androstenedione levels remained unaffected. Throughout a subgroup's meta-analysis, a significant increase in serum SHBG was observed only in those studies where MI was administered for at least 24 weeks (SMD = 0.425 nmol/L, 95% CI: 0.050-0.801, *P* = 0.026). These results highlight the beneficial effect of MI in improving the metabolic profile of women with PCOS, concomitantly reducing their hyperandrogenism.

KEYWORDS: d-chiro-inositol; inositol; insulin; myo-inositol; polycystic ovary syndrome

Zeng L, Yang K. Effectiveness of myoinositol for polycystic ovary syndrome: a systematic review and meta-analysis. ENDOCRINE. 2018;59(1):30–8.

Abstract

PURPOSE: To assess the effectiveness and safety of myoinositol for patients with PCOS.
METHODS: In this meta-analysis, data from randomized controlled trials are obtained to assess the effects of myoinositol vs. placebo or western medicine in women with PCOS. The study's registration number is CRD42017064563. The primary outcomes included total testosterone, estradiol (E2) and the homeostatic model assessment (HOMA) of insulin resistance.
RESULT: Ten trials involving 573 patients were included. The meta-analysis results show that: compared with the control group, myoinositolmay improve HOMA index (WMD -0.65; 95% CI -1.02, -0.28; P = 0. 0005) and increase the E2 level (WMD 16.16; 95% CI 2.01, 30.31; P = 0. 03); while there is no enough strong evidence that the myoinositol has an effect on the total testosterone level (WMD -16.11; 95% CI -46.08, 13.86; P = 0. 29).
CONCLUSION: Based on current evidence, myoinositol may be recommended for the treatment of PCOS with insulin resistance, as well as for improving symptoms caused by decreased estrogen in PCOS.
KEYWORDS: Meta-analysis; Myoinositol; Polycystic ovary syndrome; Systematic review

Cancer Risk

Qiang Y, Li Q, Xin Y, Fang X, Tian Y, Ma J, Wang J, Wang Q, Zhang R, Wang J, Wang F. Intake of dietary one-carbon metabolism-related b vitamins and the risk of esophageal cancer: A dose-response meta-analysis. Nutrients. 2018 Jul;10(7):835.

Abstract

Several B vitamins are essential in the one-carbon metabolism pathway, which is central to DNA methylation, synthesis, and repair. Moreover, an imbalance in this pathway has been linked to certain types of cancers. Here, we performed a meta-analysis in order to investigate the relationship between the intake of four dietary one-carbon metabolism-related B vitamins (B2, B6, folate, and B12) and the risk of esophageal cancer (EC). We searched PubMed, Web of Science, and Embase for relevant studies published through 1 March 2018. The odds ratio (OR) with 95% confidence interval (CI) for the highest versus the lowest level of each dietary B vitamin was then calculated. From 21 articles reporting 26 studies including 6404 EC cases and 504,550 controls, we found an inverse correlation between the consumption of vitamin B6 and folate and the risk of EC; this association was specific to the US, Europe, and Australia, but was not found in Asia. A dose-response analysis revealed that each 100 μg/day increase in folate intake reduced the risk of EC by 12%. Moreover, each 1 mg/day increase in vitamin B6 intake decreased the risk of EC by 16%. Surprisingly, we found that each 1 μg/day increase in vitamin B12 intake increased the risk of esophageal adenocarcinoma by 2%, particularly in the US and Europe, suggesting both geographic and histological differences. Together, our results suggest that an increased intake of one-carbon metabolism-related B vitamins may protect against EC, with the exception of vitamin B12, which should be consumed in moderation.

Shuai Ben, Mulong Du, Gaoxiang Ma, Jianhua Qu, Liyang Zhu, Haiyan Chu, et al. Vitamin B2 intake reduces the risk for colorectal cancer: a dose-response analysis. European Journal of Nutrition [Internet]. 2019 Jun 1 [cited 2019 Sep 22];58(4):1591–602.

Abstract

PURPOSE: Several epidemiological studies have assessed the ability of vitamin B2 to prevent colorectal cancer (CRC), but the results are controversial results. We conducted a dose-response meta-analysis to investigate the association between vitamin B2 and CRC risk.
METHODS: We searched the PubMed and EMBASE database until January 3, 2018 to identify relevant studies. The pooled relative risks (RRs) with the corresponding 95% confidence intervals (CIs) were calculated using a random-effects model or fixed-effects model. The dose-response relationship was assessed by restricted cubic splines.
RESULTS: A total of 14 studies reporting vitamin B2 intake and two studies reporting blood vitamin B2 concentration, comprising 14,934 cases and 1593 cases, respectively, were

included in the meta-analysis. Vitamin B2 intake was inversely associated with CRC risk (RR = 0.87; 95% CI 0.81-0.93). Similar results were found for total vitamin B2 intake from diet and supplements (RR = 0.86; 95% CI 0.78-0.94) and dietary vitamin B2 intake (RR = 0.89, 95% CI 0.82-0.98) in subgroup analyses. The dose-response model indicated a non-linear trend, and CRC risk was reduced by 10% when vitamin B2 intake increased to 5 mg/day. In addition, high blood concentrations of vitamin B2 could also reduce the CRC risk (RR = 0.74; 95% CI 0.59-0.92).
CONCLUSIONS: This dose-response analysis indicates that vitamin B2 intake is inversely associated with CRC risk. The inverse association may also exist between blood vitamin B2 concentration and CRC risk. These results suggest the importance of vitamin B2 intake in the prevention of CRC.
KEYWORDS: Colorectal cancer; Dose–response; Meta-analysis; Vitamin B2

Yang J, Li JH, Deng BH, Wang QZ. Association of One-Carbon Metabolism-Related Vitamins (Folate, B6, B12), homocysteine and methionine with the risk of lung cancer: systematic review and meta-analysis. Frontiers in oncology. 2018;8:493.

Abstract

BACKGROUND: Studies on serum one-carbon metabolism factors (folate, B6, B12, homocysteine, and methionine) with lung cancer (LC) risk have produced inconsistent results. We aimed to systematically evaluate the association between them.
METHODS: This study was reported in accordance with the PRISMA Statement and was registered with PROSPERO (no. CRD42018086654). Relevant studies were searched in PubMed, Embase, MEDLINE, and CNKI up to February 2018. Random-effects models were used to estimate the pooled standardized mean differences (SMD) or odds ratios (OR), as well as their 95% confidence interval (CI). Sensitivity and subgroup analysis were performed to identify the source of heterogeneity. Publication bias was also assessed.
RESULTS: A total of 14 articles (8,097 patients) were included. The concentration of serum folate and vitamin B6 of LC patients were lower than the controls [SMD -0.53, 95% CI (-0.70, -0.35), p = 0.001 and SMD -0.28, 95%CI (-0.53, -0.02), p = 0.001, respectively]. While the concentration of homocysteine of the cases was higher than the controls [SMD 0.41, 95% CI (0.24, 0.59), p = 0.001]. However, there were no significant differences between LC patients and the controls in terms of vitamin B12 and methionine [SMD -0.09, 95% CI (-0.27, 0.09), p = 0.202 and SMD -0.13, 95% CI (-0.36, 0.10), p = 0.001]. Subgroup analysis showed that these results were more significant in Europe, Asia, former and current smokers, and the male population (p-value < 0.05).
CONCLUSIONS: Serum folate and vitamin B6 might be protective factors against lung carcinogenesis and homocysteine could contribute to LC risk.

KEYWORDS: folate (vitamin B9); lung cancer; meta-analysis; one-carbon metabolism; serum; vitamin B6

Neurological Disorders

Thompson DF, Saluja HS. Prophylaxis of migraine headaches with riboflavin: a systematic review. J Clin Pharm Ther. 2017 Aug;42(4):394–403. doi: 10.1111/jcpt.12548.

Abstract

WHAT IS KNOWN AND OBJECTIVE: Migraine headache is a relatively common, debilitating condition that costs our healthcare system over 78 billion dollars per year. Riboflavin has been advocated as a safe, effective prophylactic therapy for the prevention of migraines. The purpose of this study was to provide a systematic review of the current role of riboflavin in the prophylaxis of migraine headache.
METHODS: A MEDLINE literature search inclusive of the dates 1966-2016 was performed using the search terms: riboflavin and migraine disorders. Excerpta Medica was searched from 1980 to 2016 using the search terms: riboflavin and migraine. Additionally, Web of Science was searched using the terms riboflavin and migraine inclusive of 1945-2016. Bibliographies of all relevant papers were reviewed for additional citations. We utilized the PRISMA guidelines to select English language, human, clinical trials of riboflavin as a single entity or in combination, review articles, and supporting pharmacokinetic and pharmacogenomic data assessing the efficacy and mechanism of riboflavin therapy in the prophylactic treatment of migraine headache.
RESULTS AND DISCUSSION: A total of 11 clinical trials reveal a mixed effect of riboflavin in the prophylaxis of migraine headache. Five clinical trials show a consistent positive therapeutic effect in adults; four clinical trials show a mixed effect in paediatric and adolescent patients, and two clinical trials of combination therapy have not shown benefit. Adverse reactions with riboflavin have generally been mild.
WHAT IS NEW AND CONCLUSION: Riboflavin is well tolerated, inexpensive and has demonstrated efficacy in the reduction of adult patient's migraine headache frequency. Additional data are needed, however, to resolve questions involving pharmacokinetic issues and pharmacogenomic implications of therapy.

KEYWORDS: migraine; pharmacogenomics; pharmacokinetics; riboflavin

Wang JY, Wu YH, Liu SJ, Lin YS, Lu PH. Vitamin B12 for herpetic neuralgia: A meta-analysis of randomised controlled trials. Complementary therapies in medicine. 2018 Dec 1;41:277-82.

Abstract

BACKGROUND: Postherpetic neuralgia (PHN) is the most distressful complication of herpes zoster. PHN results in an impaired quality of life and higher healthcare utilization. Vitamin B12 has been proven to be effective in pain relief for various conditions.
OBJECTIVE: We conducted a systematic review and a meta-analysis to evaluate the efficacy of vitamin B12 supplementation in PHN patients.
METHODS: PubMed, Embase, Cochrane Library, CINAHL, and ClinicalTrials.gov registry were searched. Randomised control trials evaluating the efficacy and safety of vitamin B12 in PHN patients were selected. Eligible trials were abstracted and assessed for the risk of bias by two reviewers, and the results of pain indicators in the selected trials were analysed.

RESULTS: Four trials including 383 participants were published between 2013 and 2016. Compared with the placebo group, the Vitamin B12 group exhibited a significant decrease in the Numeric Rating Scale score, with a mean difference of -4.01 (95% confidence interval = -4.70 to -3.33). Vitamin B12 administration improved the quality of life of PHN patients with moderate quality evidence and significantly decreased the number of patients using analgesics.
CONCLUSION: Vitamin B12 appears to be an attractive complementary therapy for PHN patients. Further investigation is needed before conclusive recommendations can be made.
KEYWORDS: Herpetic neuralgia; Vitamin B12

Jiang DQ, Zhao SH, Li MX, Jiang LL, Wang Y, Wang Y. Prostaglandin E1 plus methylcobalamin combination therapy versus prostaglandin E1 monotherapy for patients with diabetic peripheral neuropathy: A meta-analysis of randomized controlled trials. Medicine. 2018 Nov;97(44).

Abstract

BACKGROUND: Prostaglandin E1 (P) or methylcobalamin (M) treatment has been suggested as a therapeutic approach for diabetic peripheral neuropathy (DPN) in many clinical trial reports. However, the combined effects of 2 drugs still remain dubious.
OBJECTIVE: The aim of this report was to evaluate the efficacy of M plus P (M+P) for the treatment of DPN compared with that of P monotherapy, in order to provide a reference resource for rational drug use.
METHODS: Randomized controlled trials (RCTs) of M+P for DPN published up to September 2017 were searched. Risk ratio (RR), mean difference (MD), and 95% confidence interval (CI) were calculated and heterogeneity was assessed with the I test. Subgroup and sensitivity analyses were also performed. The outcomes measured were as follows: the clinical efficacy, median motor nerve conduction velocities (MNCV), median sensory nerve conduction velocity (SNCV), peroneal MNCV, peroneal SNCV, and adverse effects.
RESULTS: Sixteen RCTs with 1136 participants were included. Clinical efficacy of M+P combination therapy was significantly better than P monotherapy (fifteen trials; RR 1.25, 95% CI 1.18-1.32, P<.00001, I=27%). Compared with P monotherapy, the pooled effects of M+P combination therapy on nerve conduction velocity were (MD 6.29, 95% CI 4.63-7.94, P<.00001, I=90%) for median MNCV, (MD 5.68, 95% CI 3.53-7.83, P<.00001, I=94%) for median SNCV, (MD 5.36, 95% CI 3.86-6.87, P<.00001, I=92%) for peroneal MNCV, (MD 4.62, 95% CI 3.48-5.75, P<.00001, I=86%) for peroneal SNCV. There were no serious adverse events associated with drug intervention.
CONCLUSIONS: M+P combination therapy was superior to P monotherapy for improvement of neuropathic symptoms and NCVs in DPN patients. Moreover, no serious adverse events occur in combination therapy.

Pregnancy

Akison LK, Kuo J, Reid N, Boyd RN, Moritz KM. Effect of choline supplementation on neurological, cognitive, and behavioral outcomes in

offspring arising from alcohol exposure during development: a quantitative systematic review of clinical and preclinical studies. Alcohol Clin Exp Res. 2018 Sep;42(9):1591-1611. doi: 10.1111/acer.13817.

Abstract

Prenatal alcohol exposure results in cognitive, behavioral, and neurological deficits in offspring. There is an urgent need for safe and effective treatments to overcome these effects. Maternal choline supplementation has been identified as a potential intervention. Our objective was to review preclinical and clinical studies using choline supplementation in known cases of fetal alcohol exposure to determine its effectiveness in ameliorating deficits in offspring. A systematic search of 6 electronic databases was conducted and studies selected by reviewing titles/abstracts against specific inclusion/exclusion criteria. Study characteristics, population demographics, alcohol exposure, and intervention methods were tabulated, and quality of reporting was assessed. Data on cognitive, behavioral, and neurological outcomes were extracted and tabulated. Quantitative analysis was performed to determine treatment effects for individual study outcomes. A total of 189 studies were retrieved following duplicate removal. Of these, 22 studies (2 randomized controlled trials, 2 prospective cohort studies, and 18 preclinical studies) met the full inclusion/exclusion criteria. Choline interventions were administered at different times relative to alcohol exposure, impacting on their success to prevent deficits for specific outcomes. Only 1 clinical study showed significant improvements in information processing in 6-month-old infants from mothers treated with choline during pregnancy. Preclinical studies showed significant amelioration of deficits due to prenatal alcohol exposure across a wide variety of outcomes, including epigenetic/molecular changes, gross motor, memory, and executive function. This review suggests that choline supplementation has the potential to ameliorate specific behavioral, neurological, and cognitive deficits in offspring caused by fetal alcohol exposure, at least in preclinical studies. As only 1 clinical study has shown benefit, we recommend more clinical trials be undertaken to assess the effectiveness of choline in preventing deficits across a wider range of cognitive domains in children.

KEYWORDS: Choline Supplementation; Fetal Alcohol Exposure; Fetal Alcohol Spectrum Disorder; Fetal Development; Maternal Nutrition

Guo X, Guo S, Miao Z, Li Z, Zhang H. Myo-inositol lowers the risk of developing gestational diabetic mellitus in pregnancies: A systematic review and meta-analysis of randomized controlled trials with trial sequential analysis. J Diabetes Complications. 2018 Mar;32(3):342-348. doi: 10.1016/j.jdiacomp.2017.07.007.

Abstract

AIMS: To explore the potential benefit of myo-inositol on pregnant women with high risk of developing gestational diabetes mellitus (GDM).
METHODS: Pubmed, Embase, and Cochrane library were systematically searched for randomized controlled trials (RCTs) comparing myo-inositol with placebo for pregnant

women with risk factors of GDM. Primary outcome were the incidence of GDM and birth weight. Secondary outcomes included fasting, 1h, and 2h oral glucose tolerance test (OGTT), and complications. Trial sequential analysis (TSA) was performed on primary outcomes to confirm the pooled results. Number needed to treat (NNT) was calculated to show the efficacy of myo-inositol supplement.
RESULTS: Four RCTs with 586 patients were included. Compared with placebo, patients with myo-inositol supplement had significantly lower the risk of developing GDM (RR=0.44, 95% CI [0.32, 0.62], P<0.0001) without heterogeneity (I2=0%, P=0.99), which was confirmed by TSA. NNT was 6.2 and rounded to 7. Myo-inositol did not significantly decrease birth weight (60.60g, 95% CI [-177.21, 56.02], P=0.31) with significant heterogeneity (I2=52%, P=0.12), but was not confirmed by TSA. Myo-inositol supplement was related to significantly lower fasting, 1h, and 2h OGTT value and the incidence of pre-term delivery. Difference was not significant between myo-inositol and placebo regarding incidence of other complications.
CONCLUSION: Myo-inositol is related to lower incidence of GDM, as well as fasting, 1h, and 2h OGTT value, in pregnant women with high risk of this condition. Myo-inositol might not be related to a lower birth weight, which needs further confirmation.
KEYWORDS: Gestational diabetes mellitus; Meta-analysis; Myo-inositol; Pregnant; Trial sequential analysis

Vitagliano A1, Saccone G2, Cosmi E3, Visentin S3, Dessole F4, Ambrosini G3, et al. Inositol for the prevention of gestational diabetes: a systematic review and meta-analysis of randomized controlled trials. Arch Gynecol Obstet. 2019 Jan;299(1):55-68. doi: 10.1007/s00404-018-5005-0.

Abstract

PURPOSE: Inositol (ISL) embraces a family of simple carbohydrates with insulin-sensitizing properties, whose most common isoforms are Myo-inositol (MYO) and D-chiro inositol (DCI). The aim of the present study was to assess the efficacy and safety of ISL supplementation during pregnancy for the prevention of gestational diabetes (GDM).
METHODS: We conducted a systematic literature search in electronic databases until October 2017. We included all randomized controlled trials (RCTs) comparing pregnant women with GDM who were randomized to either ISL (i.e., intervention group) or either placebo or no treatment (i.e., control group). The primary outcome was the preventive effect on GDM, defined as the rate of GDM in women without a prior diagnosis of GDM. Pooled results were expressed as odds ratio (OR) with a 95% confidence interval (95% CI).
RESULTS: Five RCTs were included (including 965 participants). ISL supplementation was associated with lower rate of GDM (OR 0.49, 95% CI 0.24-1.03, p = 0.01) and lower preterm delivery rate (OR 0.35, 95% CI 0.17-0.74, p = 0.006). No adverse effects were reported. Adjusting for the type of intervention (MYO 2 g twice daily vs MYO 1100 mg plus DCI 27.6 mg daily), a significant effect was found only in patients receiving 2 g MYO twice daily.
CONCLUSIONS: ISLs administration during pregnancy appears to be safe and may represent a novel strategy for GDM prevention. In particular, the double administration of MYO 2 g per day may improve the glycemic homeostasis and may reduce GDM rate and preterm delivery rate.

KEYWORDS: Diabetes prevention; Gestational diabetes; Inositol; Maternal–fetal health; Preterm delivery

Zhang H, Lv Y, Li Z, Sun L, Guo W. The efficacy of myo-inositol supplementation to prevent gestational diabetes onset: a meta-analysis of randomized controlled trials. The Journal Of Maternal-Fetal & Neonatal Medicine: The Official Journal Of The European Association Of Perinatal Medicine, The Federation Of Asia And Oceania Perinatal Societies, The International Society Of Perinatal Obstetricians [Internet]. 2019 Jul [cited 2019 Sep 22];32(13):2249–55.

Abstract

INTRODUCTION: The efficacy of myo-inositol supplementation to prevent gestational diabetes onset remains controversial. We conducted a systematic review and meta-analysis to explore the influence of myo-inositol supplementation on the incidence of gestational diabetes.
METHODS: We search PubMed, Embase, Web of science, EBSCO, and Cochrane Library databases through November 2017 for randomized controlled trials (RCTs) assessing the effect of myo-inositol supplementation on gestational diabetes onset. This meta-analysis is performed using the random-effect model.
RESULTS: Five randomized controlled trials (RCTs) are included in the meta-analysis. Compared with control group in pregnant women, myo-inositol supplementation is associated with significantly reduced incidence of gestational diabetes (risk ratio (RR) = 0.43; 95%CI = 0.21-0.89; p = .02), and preterm delivery (RR = 0.36; 95%CI = 0.17-0.73; p = .005), but has no substantial impact on 2-h glucose oral glucose tolerance test (OGTT) (mean difference (MD) = -6.90; 95%CI = -15.07 to 1.27; p = .10), gestational age at birth (MD = 0.74; 95%CI = -1.06 to 2.54; p = .42), birth weight (MD = -5.50; 95%CI = -116.99 to 105.99; p = .92), and macrosomia (RR = 0.65; 95%CI = 0.20-2.11; p = .47).
CONCLUSIONS: Myo-inositol supplementation has some ability to reduce the incidence of gestational diabetes and preterm delivery in pregnant women.
KEYWORDS: Myo-inositol supplementation; gestational diabetes; incidence; meta-analysis; randomized controlled trials

Neuropsychiatric Disorders

Firth J, Stubbs B, Sarris J, Rosenbaum S, Teasdale S, Berk M, Yung AR. The effects of vitamin and mineral supplementation on symptoms of schizophrenia: a systematic review and meta-analysis. Psychological medicine. 2017 Jul;47(9):1515-27.

Abstract

BACKGROUND: When used as an adjunctive with antipsychotics, certain vitamins and minerals may be effective for improving symptomatic outcomes of schizophrenia, by

restoring nutritional deficits, reducing oxidative stress, or modulating neurological pathways.
METHOD: We conducted a systematic review of all randomized controlled trials (RCTs) reporting effects of vitamin and/or mineral supplements on psychiatric symptoms in people with schizophrenia. Random-effects meta-analyses were used to calculate the standardized mean difference between nutrient and placebo treatments.
RESULTS: An electronic database search in July 2016 identified 18 eligible RCTs, with outcome data for 832 patients. Pooled effects showed that vitamin B supplementation (including B6, B8 and B12) reduced psychiatric symptoms significantly more than control conditions [g = 0.508, 95% confidence interval (CI) 0.01-1.01, p = 0.047, I 2 = 72.3%]. Similar effects were observed among vitamin B RCTs which used intention-to-treat analyses (g = 0.734, 95% CI 0.00-1.49, p = 0.051). However, no effects of B vitamins were observed in individual domains of positive and negative symptoms (both p > 0.1). Meta-regression analyses showed that shorter illness duration was associated with greater vitamin B effectiveness (p = 0.001). There were no overall effects from antioxidant vitamins, inositol or dietary minerals on psychiatric symptoms.
CONCLUSIONS: There is preliminary evidence that certain vitamin and mineral supplements may reduce psychiatric symptoms in some people with schizophrenia. Further research is needed to examine how the benefits of supplementation relate to nutrient deficits and the impact upon underlying neurobiological pathways, in order to establish optimal nutrient formulations for improving clinical outcomes in this population. Future studies should also explore the effects of combining beneficial nutrients within multi-nutrient formulas.
KEYWORDS: Adjunctive; diet; food; nutrition; psychosis

McCabe D, Lisy K, Lockwood C, Colbeck M. The impact of essential fatty acid, B vitamins, vitamin C, magnesium and zinc supplementation on stress levels in women: a systematic review. JBI Database System Rev Implement Rep. 2017 Feb;15(2):402-453. doi: 10.11124/JBISRIR-2016-002965.

Abstract

BACKGROUND: Women juggling multiple roles in our complex society are increasingly experiencing psychological stress. Dietary supplementation to manage stress is widespread despite limited supporting evidence. A systematic review of the available literature was undertaken to investigate the efficacy of specific dietary supplements in managing female stress and anxiety.
OBJECTIVES: To identify the impact of essential fatty acids (EFAs), B vitamins, vitamin C, magnesium and/or zinc, consumed as dietary supplements to the daily diet, on female stress and anxiety levels.
INCLUSION CRITERIA TYPES OF PARTICIPANTS: Women aged 18 years and over, who had participated in a study where stress and/or anxiety were assessed.
TYPES OF INTERVENTION(S): Dietary supplementation with EFAs, B vitamins, vitamin C, magnesium and/or zinc.
TYPES OF COMPARATORS: Supplements, either alone or combined, were compared with either no intervention or placebo.
TYPES OF STUDIES: Randomized controlled and pseudo-randomized trials were included.
OUTCOMES: Stress and anxiety were assessed using self-report or physiological outcome

measures.
SEARCH STRATEGY: Published and unpublished studies were sought via MEDLINE (via PubMed), Embase, Scopus, CINAHL, PsycINFO, PsycARTICLES, MedNar, National Institute of Mental Health and the International Association for Women's Mental Health.
METHODOLOGICAL QUALITY: Methodological quality was evaluated using standardized critical appraisal instruments from the Joanna Briggs Institute.
DATA EXTRACTION: Data were extracted using the standardized data extraction instruments from the Joanna Briggs Institute.
DATA SYNTHESIS: Due to heterogeneity of the included studies, narrative synthesis was performed.
RESULTS: Fourteen studies were included in this review. Essential fatty acids were effective in reducing perceived stress and salivary cortisol levels during pregnancy and anxiety in premenstrual women, and anxiety during menopause in the absence of depression, but were ineffective when depression was disregarded. Disregarding the hormonal phase, EFAs were ineffective in reducing stress or anxiety in four groups of women. Combined magnesium and vitamin B6 supplementation reduced premenstrual anxiety but had no effect when used in isolation and did not affect stress in women suffering from dysmenorrhea when combined or used in isolation. Older women experienced anxiety reduction using vitamin B6, but not folate or vitamin B12. High-dose sustained-release vitamin C was effective in reducing anxiety and blood pressure in response to stress.
CONCLUSION: The current review suggests that EFAs may be effective in reducing prenatal stress and salivary cortisol and may reduce anxiety during premenstrual syndrome and during menopause in the absence of depression. Magnesium and vitamin B6 may be effective in combination in reducing premenstrual stress, and vitamin B6 alone may reduce anxiety effectively in older women. High-dose sustained-release vitamin C may reduce anxiety and mitigate increased blood pressure in response to stress.
IMPLICATIONS FOR PRACTICE: Essential fatty acids may be effective in reducing prenatal stress and salivary cortisol levels, and premenstrual or menopausal anxiety in the absence of depression. Combining magnesium and vitamin B6 may reduce premenstrual anxiety and vitamin B6 may reduce anxiety in older women. High-dose sustained-release vitamin C may reduce anxiety and mitigate increased blood pressure in response to stress.
IMPLICATIONS FOR RESEARCH: Investigating supplementation in longer term studies is warranted and should include compliance testing, the use of inert substances as controls and reliable outcome measures.

Mukai T, Kishi T, Matsuda Y, Iwata N. A meta-analysis of inositol for depression and anxiety disorders. Hum Psychopharmacol. 2014 Jan;29(1):55-63. doi: 10.1002/hup.2369.

Abstract

OBJECTIVE: This study is a meta-analysis of inositol as a treatment for depression and anxiety disorders.
METHODS: PubMed, Cochrane Library database, and PsycINFO were searched up to 14 August 2013. A systematic review and meta-analysis of double-blind, randomized, placebo-controlled trials (RCTs) were conducted comparing inositol for depressed or anxiety disorder patients.

RESULTS: Seven RCTs in depression (two bipolar depression studies, one bipolar depression and major depressive disorder (MDD) study, two MDD studies, and two premenstrual dysphoric disorder (PMDD) studies) (n = 242) were identified. Four RCTs in anxiety disorders (two obsessive-compulsive disorder studies, one panic disorder study, and one posttraumatic stress disorder study) (n = 70) were also identified. There were no statistically significant effects of inositol on depressive, anxiety, and obsessive-compulsive symptoms and discontinuation (all-cause, side effects, and worsening psychiatric symptoms). However, inositol had marginally more responders in depression than placebo (p = 0.06), and inositol showed a trend towards superior efficacy for depressive symptoms in patients with PMDD (p = 0.07). Inositol marginally caused gastrointestinal upset compared with placebo (p = 0.06).
CONCLUSIONS: Our results suggest that inositol may be beneficial for depressed patients, especially those with PMDD. The main limitation of this report is that a small number of studies were included in this meta-analysis.

Sakuma K, Matsunaga S, Nomura I, Okuya M, Kishi T, Iwata N. Folic acid/methylfolate for the treatment of psychopathology in schizophrenia: a systematic review and meta-analysis. Psychopharmacology. 2018 Aug 1;235(8):2303-14.

Abstract

RATIONALE: This study aims to examine whether folate/folic acid/methylfolate/folinic acid supplemented to antipsychotics (FA + AP) is beneficial in schizophrenia treatment.
OBJECTIVE: We conducted a comprehensive systematic review and meta-analysis of double-blind, placebo-controlled, randomized clinical trials (RCTs) of FA + AP for schizophrenia.
METHODS: The primary outcome was an improvement in total symptoms. Other outcomes were psychopathology subscales (positive, negative, general, and depressive symptoms), discontinuation due to all-cause and adverse events, and individual adverse events. The meta-analysis evaluated the effect size based on a random-effects model.
RESULTS: Although we included ten RCTs with 925 patients in total (seven folic acid RCTs (n = 789), two methylfolate RCTs (n = 96), and one folinic acid RCT (n = 40)) in the systematic review, only seven RCTs were included in the meta-analysis. Pooled FA + AP treatments were not superior to placebo + AP in the improvement of total (N = 7, n = 340; standardized mean difference (SMD) = - 0.20, 95% confidence interval (CI) = - 0.41, 0.02, p = 0.08, I2 = 0%), positive, general, or depressive symptoms. Pooled FA + AP treatments were more effective than placebo + AP for negative symptoms (N = 5, n = 281; SMD = -0.25, 95% CI = -0.49, -0.01, p = 0.04, I2 = 0%). Although pooled FA + AP treatments were associated with a lower incidence of serious adverse events than placebo treatments (N = 4, n = 241; risk ratio = 0.32, 95% CI = 0.12-0.82, p = 0.02, I2 = 0%; number needed to harm = not significant), there were no significant differences in other safety outcomes between both treatments.
CONCLUSIONS: Our findings suggest that pooled FA + AP treatment improves negative symptoms in schizophrenia patients. Moreover, this treatment was well tolerated. However, because our results might exhibit a small-study effect, future studies with a larger sample should be conducted to obtain more robust results.

KEYWORDS: Folic acid; Meta-analysis; Methylfolate; Negative symptoms; Schizophrenia; Systematic review

Sarris J, Murphy J, Mischoulon D, Papakostas GI, Fava M, Berk M, Ng CH. Adjunctive nutraceuticals for depression: a systematic review and meta-analyses. American Journal of Psychiatry. 2016 Apr 26;173(6):575-87.

Abstract

OBJECTIVE: There is burgeoning interest in augmentation strategies for improving inadequate response to antidepressants. The adjunctive use of standardized pharmaceutical-grade nutrients, known as nutraceuticals, has the potential to modulate several neurochemical pathways implicated in depression. While many studies have been conducted in this area, to date no specialized systematic review (or meta-analysis) has been conducted.
METHOD: A systematic search of PubMed, CINAHL, Cochrane Library, and Web of Science was conducted up to December 2015 for clinical trials using adjunctive nutrients for depression. Where sufficient data were available, a random-effects model analyzed the standard mean difference between treatment and placebo in the change from baseline to endpoint, combining the effect size data. Funnel plot and heterogeneity analyses were also performed.
RESULTS: Primarily positive results were found for replicated studies testing S-adenosylmethionine (SAMe), methylfolate, omega-3 (primarily EPA or ethyl-EPA), and vitamin D, with positive isolated studies for creatine, folinic acid, and an amino acid combination. Mixed results were found for zinc, folic acid, vitamin C, and tryptophan, with nonsignificant results for inositol. No major adverse effects were noted in the studies (aside from minor digestive disturbance). A meta-analysis of adjunctive omega-3 versus placebo revealed a significant and moderate to strong effect in favor of omega-3. Conversely, a meta-analysis of folic acid revealed a nonsignificant difference from placebo. Marked study heterogeneity was found in a Higgins test for both omega-3 and folic acid studies; funnel plots also revealed asymmetry (reflecting potential study bias).
CONCLUSIONS: Current evidence supports adjunctive use of SAMe, methylfolate, omega-3, and vitamin D with antidepressants to reduce depressive symptoms.

Veronese N, Stubbs B, Solmi M, Ajnakina O, Carvalho AF, Maggi S. Acetyl-l-carnitine supplementation and the treatment of depressive symptoms: A systematic review and meta-analysis. Psychosomatic medicine. 2018 Feb 1;80(2):154-9.

Abstract

OBJECTIVE: Deficiency of acetyl-L-carnitine (ALC) seems to play a role in the risk of developing depression, indicating a dysregulation of fatty acid transport across the inner membrane of mitochondria. However, data about ALC supplementation in humans are limited. We thus conducted a systematic review and meta-analysis investigating the effect

of ALC on depressive symptoms across randomized controlled trials (RCTs).
METHODS: A literature search in major databases, without language restriction, was undertaken from inception until 30 December 2016. Eligible studies were RCTs of ALC alone or in combination with antidepressant medications, with a control group taking placebo/no intervention or antidepressants. Standardized mean differences (SMDs) and 95% confidence intervals (CIs) were used for summarizing outcomes with a random-effect model.
RESULTS: Twelve RCTs (11 of which were ALC monotherapy) with a total of 791 participants (mean age = 54 years, % female = 65%) were included. Pooled data across nine RCTs (231 treated with ALC versus 216 treated with placebo and 20 no intervention) showed that ALC significantly reduced depressive symptoms (SMD = -1.10, 95% CI = -1.65 to -0.56, I = 86%). In three RCTs comparing ALC versus antidepressants (162 for each group), ALC demonstrated similar effectiveness compared with established antidepressants in reducing depressive symptoms (SMD = 0.06, 95% CI = -0.22 to 0.34, I = 31%). In these latter RCTs, the incidence of adverse effects was significantly lower in the ALC group than in the antidepressant group. Subgroup analyses suggested that ALC was most efficacious in older adults.
CONCLUSIONS: ALC supplementation significantly decreases depressive symptoms compared with placebo/no intervention, while offering a comparable effect with that of established antidepressant agents with fewer adverse effects. Future large scale trials are required to confirm/refute these findings.

RANDOMISED CONTROLLED TRIALS

Cardiometabolic Risk and Disorders

Spence JD, Yi Q, Hankey GJ. B vitamins in stroke prevention: time to reconsider. The Lancet Neurology. 2017 Sep 1;16(9):750-60.

Abstract

B vitamin therapy lowers plasma total homocysteine concentrations, and might be a beneficial intervention for stroke prevention; however, cyanocobalamin (a form of vitamin B12) can accelerate decline in renal function and increase the risk of cardiovascular events in patients with impaired renal function. Although early trials did not show benefit in reduction of stroke, these results might have been due to harm in participants with impaired renal function. In patients with diabetic nephropathy, cyanocobalamin is harmful, whereas B vitamins appear to reduce cardiovascular events in study participants with normal renal function. Our meta-analysis of individual patient data from two large trials of B vitamin therapy (VISP and VITATOPS) indicates that patients with impaired renal function who are exposed to high-dose cyanocobalamin do not benefit from therapy with B vitamins for the prevention of stroke (risk ratio 1·04, 95% CI 0·84-1·27), however, patients with normal renal function who are not exposed to high-dose cyanocobalamin benefit significantly from this treatment (0.78, 0·67-0·90; interaction p=0·03). The potential benefits of B vitamin therapy with folic

acid and methylcobalamin or hydroxycobalamin, instead of cyanocobalamin, to lower homocysteine concentrations in people at high risk of stroke warrant further investigation.

Gastrointestinal Disorders

Burr NE, Hull MA, Subramanian V. Folic acid supplementation may reduce colorectal cancer risk in patients with inflammatory bowel disease. Journal of clinical gastroenterology. 2017 Mar 1;51(3):247-53.

Abstract

GOALS: To evaluate the role of folic acid supplementation in colorectal cancer (CRC) chemoprevention in patients with inflammatory bowel disease (IBD).
BACKGROUND: CRC is a serious complication of IBD. Folic acid supplementation has been shown to be chemopreventative in sporadic CRC. Patients with IBD are at risk of folate deficiency though intestinal malabsorption and also competitive inhibition by concurrent sulfasalazine use. To date, there have been several studies reporting on folic acid supplementation in patients with IBD and CRC.
STUDY: We searched electronic databases for studies reporting folic acid use and CRC incidence in patients with IBD. We produced a pooled hazard ratio with 95% confidence intervals using a random-effects model. Preplanned subgroup analyses were performed to explore for any potential sources of heterogeneity.
RESULTS: Ten studies reporting on 4517 patients were included. We found an overall protective effect for folic acid supplementation on the development of CRC, pooled hazard ratio=0.58 (95% confidence interval, 0.37-0.80). There was low to moderate heterogeneity among studies, I=29.7%. Subgroup analyses suggested that folic acid use was protective in hospital-based studies, studies from North America and those that were performed before folate fortification of foods in 1998.
CONCLUSIONS: CRC remains an important complication of IBD. Chemoprevention is an attractive strategy and folic acid as a cheap, safe, and well-tolerated supplement may have a role. Focused prospective studies are required to precisely define any potential effect.

Cancer Risk and Support

Chen AC, Martin AJ, Choy B, Fernández-Peñas P, Dalziell RA, McKenzie CA et al. A phase 3 randomized trial of nicotinamide for skin-cancer chemoprevention. N Engl J Med. 2015 Oct 22;373(17):1618-26. doi: 10.1056/NEJMoa1506197.

Abstract

BACKGROUND: Nonmelanoma skin cancers, such as basal-cell carcinoma and squamous-cell carcinoma, are common cancers that are caused principally by ultraviolet (UV) radiation. Nicotinamide (vitamin B3) has been shown to have protective effects against damage caused by UV radiation and to reduce the rate of new premalignant actinic keratoses.
METHODS: In this phase 3, double-blind, randomized, controlled trial, we randomly

assigned, in a 1:1 ratio, 386 participants who had had at least two nonmelanoma skin cancers in the previous 5 years to receive 500 mg of nicotinamide twice daily or placebo for 12 months. Participants were evaluated by dermatologists at 3-month intervals for 18 months. The primary end point was the number of new nonmelanoma skin cancers (i.e., basal-cell carcinomas plus squamous-cell carcinomas) during the 12-month intervention period. Secondary end points included the number of new squamous-cell carcinomas and basal-cell carcinomas and the number of actinic keratoses during the 12-month intervention period, the number of nonmelanoma skin cancers in the 6-month postintervention period, and the safety of nicotinamide.
RESULTS: At 12 months, the rate of new nonmelanoma skin cancers was lower by 23% (95% confidence interval [CI], 4 to 38) in the nicotinamide group than in the placebo group (P=0.02). Similar differences were found between the nicotinamide group and the placebo group with respect to new basal-cell carcinomas (20% [95% CI, -6 to 39] lower rate with nicotinamide, P=0.12) and new squamous-cell carcinomas (30% [95% CI, 0 to 51] lower rate, P=0.05). The number of actinic keratoses was 11% lower in the nicotinamide group than in the placebo group at 3 months (P=0.01), 14% lower at 6 months (P<0.001), 20% lower at 9 months (P<0.001), and 13% lower at 12 months (P=0.001). No noteworthy between-group differences were found with respect to the number or types of adverse events during the 12-month intervention period, and there was no evidence of benefit after nicotinamide was discontinued.
CONCLUSIONS: Oral nicotinamide was safe and effective in reducing the rates of new nonmelanoma skin cancers and actinic keratoses in high-risk patients. (Funded by the National Health and Medical Research Council; ONTRAC Australian New Zealand Clinical Trials Registry number, ACTRN12612000625875.).

Miranti EH, Stolzenberg-Solomon R, Weinstein SJ, Selhub J, Mannisto S, Taylor PR, et al. Low vitamin B12 increases risk of gastric cancer: a prospective study of one-carbon metabolism nutrients and risk of upper gastrointestinal tract cancer. Int J Cancer [Internet]. 2017 Sep 1;141(6):1120–9.

Abstract

Previous studies have found associations between one-carbon metabolism nutrients and risk of several cancers, but little is known regarding upper gastrointestinal tract (UGI) cancer. We analyzed prediagnostic serum concentrations of several one-carbon metabolism nutrients (vitamin B12, folate, vitamin B6, riboflavin and homocysteine) in a nested case-control study within the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study of male smokers, which was undertaken in Finland between 1985 and 1988. We conducted a nested case-control study including 127 noncardia gastric adenocarcinoma (NCGA), 41 esophagogastric junctional adenocarcinoma and 60 esophageal squamous cell carcinoma incident cases identified within ATBC. Controls were matched to cases on age, date of serum collection and follow-up time. One-carbon nutrient concentrations were measured in fasting serum samples collected at baseline (up to 17 years prior to cancer diagnosis). Odds ratios and 95% confidence intervals (CI) were calculated using conditional logistic regression. Lower prediagnostic vitamin B12 concentrations at baseline were associated with a 5.8-fold increased risk of NCGA (95%

CI = 2.7-12.6 for lowest compared to highest quartile, p-trend <0.001). This association remained in participants who developed cancer more than 10 years after blood collection, and after restricting the analysis to participants with clinically normal serum vitamin B12 (>300 pmol/L). In contrast, pepsinogen I, a known serologic marker of gastric atrophy, was not associated with NCGA in this population. As vitamin B12 absorption requires intact gastric mucosa to produce acid and intrinsic factor, our findings suggest vitamin B12 as a possible serologic marker for the atrophic gastritis that precedes NCGA, one more strongly associated with subsequent NCGA than pepsinogen.

KEYWORDS: esophageal cancer; gastric atrophy; gastric cancer; one-carbon metabolism; vitamin B12

Neurological Disorders

Askari G, Nasiri M, Mozaffari-Khosravi H, Rezaie M, Bagheri-Bidakhavidi M, Sadeghi O. The effects of folic acid and pyridoxine supplementation on characteristics of migraine attacks in migraine patients with aura: A double-blind, randomized placebo-controlled, clinical trial. Nutrition. 2017 Jun;38:74-79. doi: 10.1016/j.nut.2017.01.007.

Abstract

OBJECTIVE: The aim of this study was to assess the effects of folic acid alone and in combination with pyridoxine on characteristics of migraine attacks in adult migraine patients with aura.
METHODS: This double-blind, randomized placebo-controlled, clinical trial was conducted on 95 migraine patients with aura (age range 18-65 y) in Isfahan, Islamic Republic of Iran, in 2014. Patients were randomly allocated to receive folic acid (5 mg/d) plus pyridoxine (80 mg/d) or folic acid alone (5 mg/d) or placebo (lactose) for 3 mo. Characteristics of migraine attacks including headache severity, attacks frequency, duration, and headache diary results (HDRs) were obtained for each patient at baseline and at the end of the study.
RESULTS: Folic acid plus pyridoxine intake resulted in a significant decrease compared with placebo in headache severity (-2.71 ± 0.08 versus -2.19 ± 0.05; P < 0.001), attack frequency (-3.35 ± 0.09 versus -2.73 ± 0.05; P < 0.001), duration (-7.25 ± 0.17 versus -6.5 ± 0.07; P < 0.001), and HDR (-74.15 ± 0.2 versus -72.73 ± 0.1; P < 0.001). Additionally, the reduction in these characteristics of migraine attacks in the folic acid plus pyridoxine group was significant compared with the group given folic acid alone (P < 0.001). However, these beneficial effects of the combined supplement became nonsignificant for attack duration compared with the folic acid-only and placebo groups after controlling for confounders. Folic acid intake without pyridoxine did not lead to a significant decrease in characteristics of migraine attacks compared with placebo group.
CONCLUSIONS: Supplementation of folic acid with pyridoxine could decrease the characteristics of migraine attacks including headache severity, attack frequency, and HDR; however, further studies are needed to shed light on the findings of the present study.
KEYWORDS: Folic acid; Headache; Migraine; Pyridoxine

Menon S1, Lea RA, Ingle S, Sutherland M, Wee S, Haupt LM. Effects of dietary folate intake on migraine disability and frequency. Headache. 2015 Feb;55(2):301-9. doi: 10.1111/head.12490. Epub 2015 Jan 19.

Abstract

BACKGROUND: Migraine is a highly disabling disease affecting a significant proportion of the Australian population. The methylenetetrahydrofolate reductase (MTHFR) C677T variant has been associated with increased levels of homocysteine and risk of migraine with aura (MA). Folic acid (FA), vitamin B6, and B12 supplementation has been previously shown to reduce increased levels of homocysteine and decrease migraine symptoms. However, the influence of dietary folate intake on migraine has been unclear. The aim of the current study was to analyze the association of dietary folate intake in the form of dietary folate equivalent, FA, and total food folate (TFF) on migraine frequency, severity, and disability.
METHODS: A cohort of 141 adult females of Caucasian descent with MA was genotyped for the MTHFR C677T variant using restriction enzyme digestion. Dietary folate information was collected from all participants and analyzed using the "FoodWorks" 2009 package. Folate consumption was compared with migraine frequency, severity, and disability using linear regression.
RESULTS: A significant inverse relation was observed between dietary folate equivalent ($R(2) = 0.201$, $B = -0.002$, $P = .045$, 95% confidence interval [CI] [-0.004, -0.001]) and FA ($R(2) = 0.255$, $B = -0.005$, $P = .036$, 95% CI [-0.009, -0.002]) consumption and migraine frequency. It was also observed that in individuals with the CC genotype for the MTHFR C677T variant, migraine frequency was significantly linked to FA consumption ($R(2) = 0.106$, $B = -0.004$, $P = .029$, 95% CI [-0.007, -0.004]).
CONCLUSIONS: The results from this study indicate that folate intake in the form of FA may influence migraine frequency in female MA sufferers.
KEYWORDS: dietary folate equivalent; folic acid; homocysteine; methylenetetrahydrofolate reductase C677T; migraine with aura

Neuropsychiatric Disorders

Chen H, Liu S, Ji L, Wu T, Ji Y, Zhou Y, et al. Folic acid supplementation mitigates Alzheimer's disease by reducing inflammation: a randomized controlled trial. Mediators Inflamm. 2016;2016:5912146. doi: 10.1155/2016/5912146. Epub 2016 Jun 2.

Abstract

BACKGROUND/AIMS: Low serum folate levels can alter inflammatory reactions. Both phenomena have been linked to Alzheimer's disease (AD), but the effect of folic acid on AD itself is unclear. We quantified folate supplementation's effect on inflammation and cognitive function in patients with AD over the course of 6 months.
METHODS: Patients newly diagnosed with AD (age > 60 years; n = 121; mild to severe; international criteria) and being treated with donepezil were randomly assigned into two groups with (intervention group) or without (control group) supplemental treatment with folic acid (1.25 mg/d) for 6 months. The Mini-Mental State Examination (MMSE) was

administered to all patients at baseline and follow-up, and blood samples were taken before and after treatment. We quantified serum folate, amyloid beta (Aβ), interleukin-6 (IL-6), tumor necrosis factor α (TNFα), plasma homocysteine (Hcy), S-adenosylmethionine (SAM), S-adenosylhomocysteine (SAH), and the mRNA levels of presenilin (PS), IL-6, and TNFα in leukocytes. Data were analyzed using a repeated-measures mixed model.
RESULTS: The mean MMSE was slightly increased in the intervention group compared to that in the control group ($P < 0.05$). Posttreatment, plasma SAM and SAM/SAH levels were significantly higher ($P < 0.05$), while Aβ 40, PS1-mRNA, and TNFα-mRNA levels were lower in the intervention group than in the control group ($P < 0.05$). The Aβ 42/Aβ 40 ratio was also higher in the intervention group ($P < 0.05$).
CONCLUSIONS: Folic acid is beneficial in patients with AD. Inflammation may play an important role in the interaction between folic acid and AD. This trial is registered with clinical trial registration number ChiCTR-TRC-13003246.

Hendren RL, James SJ, Widjaja F, Lawton B, Rosenblatt A, Bent S. Randomized, Placebo-Controlled Trial of Methyl B12 for Children with Autism. J Child Adolesc Psychopharmacol. 2016 Nov;26(9):774-783.

Abstract

OBJECTIVE: Children with autism spectrum disorder (ASD) have been reported to have reduced ability to methylate DNA and elevated markers of oxidative stress. We sought to determine if methyl B12, a key metabolic cofactor for cellular methylation reactions and antioxidant defense, could improve symptoms of ASD.
METHODS: A total of 57 children with ASD were randomly assigned to 8 weeks of treatment with methyl B12 (75 µg/kg) or saline placebo every 3 days in a subcutaneous injection. The primary outcome measure was overall improvement in symptoms of ASD as measured by the Clinical Global Impressions-Improvement (CGI-I) score. Secondary outcome measures included changes in the Aberrant Behavior Checklist (ABC) and the Social Responsiveness Scale (SRS). Laboratory measures of methionine methylation and antioxidant glutathione metabolism were assessed at baseline and 8 weeks.
RESULTS: A total of 50 children (mean age 5.3 years, 79% male) completed the study. The primary outcome measure - the clinician rated CGI-I score - was statistically significantly better (lower) in the methyl B12 group (2.4) than in the placebo group (3.1) (0.7 greater improvement in the methyl B12 group, 95% CI 1.2-0.2, $p = 0.005$). Clinical improvement among children treated with methyl B12 was positively correlated with increases in plasma methionine ($p = 0.05$), decreases in S-adenosyl-l-homocysteine (SAH) ($p = 0.007$) and improvements in the ratio of S-adenosylmethionine (SAM) to SAH ($p = 0.007$), indicating an improvement in cellular methylation capacity. No improvements were observed in the parent-rated ABC or SRS.
CONCLUSIONS: Methyl B12 treatment improved clinician-rated symptoms of ASD that were correlated with improvements in measures of methionine metabolism and cellular methylation capacity. Clinical Trial Registry: Efficacy Study of Subcutaneous Methyl B12 in Children with Autism: NCT01039792 (clinicaltrials.gov1).
KEYWORDS: alternative medicine; autism; nutritional supplement

Roffman JL, Petruzzi LJ, Tanner AS, Brown HE, Eryilmaz H, Ho NF, et al. Biochemical, physiological and clinical effects of L-methylfolate in

schizophrenia: a randomized controlled trial. Mol Psychiatry. 2018 Feb;23(2):316-322. doi: 10.1038/mp.2017.41.

Abstract

Folic acid supplementation confers modest benefit in schizophrenia, but its effectiveness is influenced by common genetic variants in the folate pathway that hinder conversion to its active form. We examined physiological and clinical effects of l-methylfolate, the fully reduced and bioactive form of folate, in schizophrenia. In this randomized, double-blind trial, outpatients with schizophrenia (n=55) received l-methylfolate 15 mg or placebo for 12 weeks. Patients were maintained on stable doses of antipsychotic medications. The pre-defined primary outcome was change in plasma methylfolate at 12 weeks. Secondary outcomes included change in symptoms (Positive and Negative Syndrome Scale (PANSS), Scale for Assessment of Negative Symptoms, Calgary Depression Scale for Schizophrenia), cognition (Measurement and Treatment Research to Improve Cognition in Schizophrenia composite) and three complementary magnetic resonance imaging measures (working memory-related activation, resting connectivity, cortical thickness). Primary, mixed model, intent-to-treat analyses covaried for six genetic variants in the folate pathway previously associated with symptom severity and/or response to folate supplementation. Analyses were repeated without covariates to evaluate dependence on genotype. Compared with placebo, l-methylfolate increased plasma methylfolate levels (d=1.00, P=0.0009) and improved PANSS Total (d=0.61, P=0.03) as well as PANSS Negative and General Psychopathology subscales. Although PANSS Total and General Psychopathology changes were influenced by genotype, significant PANSS Negative changes occurred regardless of genotype. No treatment differences were seen in other symptom rating scales or cognitive composite scores. Patients receiving l-methylfolate exhibited convergent changes in ventromedial prefrontal physiology, including increased task-induced deactivation, altered limbic connectivity and increased cortical thickness. In conclusion, l-methylfolate supplementation was associated with salutary physiological changes and selective symptomatic improvement in this study of schizophrenia patients, warranting larger clinical trials. ClinicalTrials.gov, NCT01091506.

Reproductive Disorders and Fertility

Fruzzetti F, Perini D, Russo M, Bucci F, Gadducci A. Comparison of two insulin sensitizers, metformin and myo-inositol, in women with polycystic ovary syndrome (PCOS). Gynecol Endocrinol. 2017 Jan;33(1):39-42. doi: 10.1080/09513590.2016.1236078.

Abstract

Insulin resistance (IR) plays a pivotal role in PCOS. Insulin-sensitizer agents such as metformin and inositols have been shown to improve the endocrine and metabolic aspects of PCOS. The purpose of this study is to compare their effects on the clinical and metabolic features of the women with PCOS. Fifty PCOS women with IR and/or hyperinsulinemia were randomized to treatment with metformin (1500 mg/day) or myo-inositol (4 g/day). IR was defined as HOMA-IR >2.5, while hyperinsulinemia was defined as a value of AUC for insulin after a glucose load over the cutoff of our laboratory obtained in normal women. The

Matsusa Index has been calculated. The women have been evaluated for insulin secretion, BMI, menstrual cycle length, acne and hirsutism, at baseline and after 6 months of therapy. The results obtained in both groups were similar. The insulin sensitivity improved in both treatment groups. The BMI significantly decreased and the menstrual cycle was normalized in about 50% of the women. No significant changes in acne and hirsutism were observed. The two insulin-sensitizers, metformin and myo-inositol, show to be useful in PCOS women in lowering BMI and ameliorating insulin sensitivity, and improving menstrual cycle without significant differences between the two treatments.
KEYWORDS: Androgens; amenorrhea; insulin resistance; insulin sensitizer; polycystic ovary syndrome

Jamilian M, Farhat P, Foroozanfard F, Afshar Ebrahimi F, Aghadavod E, Bahmani F, et al. Comparison of myo-inositol and metformin on clinical, metabolic and genetic parameters in polycystic ovary syndrome: A randomized controlled clinical trial. Clin Endocrinol (Oxf). 2017 Aug;87(2):194-200. doi: 10.1111/cen.13366.

Abstract

OBJECTIVE: To our knowledge, data on comparison of myo-inositol and metformin on clinical, metabolic and genetic parameters in subjects with polycystic ovary syndrome (PCOS) are limited. This study was carried out to compare myo-inositol and metformin on clinical, metabolic and genetic parameters in subjects with PCOS.
DESIGN, PATIENTS AND MEASUREMENTS: This randomized controlled trial was conducted among 60 subjects with PCOS aged 18-40 years. Subjects were randomly allocated into two groups to receive either myo-inositol (N=30) or metformin (N=30) for 12 weeks. Gene expression of inflammatory cytokines was assessed in peripheral blood mononuclear cells (PBMCs) of PCOS women by RT-PCR.
RESULTS: After the 12-week intervention, compared with metformin, myo-inositol intake significantly decreased serum total testosterone (-1.4±4.2 vs +0.7±1.4 nmol/L, P=.03), modified Ferriman-Gallwey (mF-G) scores (-1.1±0.7 vs -0.5±0.8, P=.01) and serum high-sensitivity C-reactive protein (hs-CRP) levels (-2.6±3.9 vs +0.2±1.5 mg/L, P<.001). RT-PCR demonstrated that compared with metformin, myo-inositol downregulated gene expression of interleukin-1 (IL-1) (P=.02) in PBMCs of subjects with PCOS. We did not observe any significant effect of myo-inositol intake compared with metformin on other hormonal profiles, plasma nitric oxide (NO) or gene expression of IL-8 and tumour necrosis factor alpha (TNF-α).
CONCLUSIONS: Overall, taking myo-inositol, compared with metformin, for 12 weeks in patients with PCOS with hyperinsulinism and normoinsulinism had beneficial effects on total testosterone, mFG scores, serum hs-CRP levels and gene expression of IL-1, but did not affect other hormonal profiles, NO levels or gene expression of IL-8 and TNF-α.
KEYWORDS: hormonal status; inflammation; metformin; myo-inositol; oxidative stress; polycystic ovary syndrome

Pregnancy

Caudill MA, Strupp BJ, Muscalu L, Nevins JEH, Canfield RL. Maternal choline supplementation during the third trimester of pregnancy improves infant information processing speed: a randomized, double-blind, controlled feeding study. FASEB J. 2018 Apr;32(4):2172-2180. doi: 10.1096/fj.201700692RR.

Abstract

Rodent studies demonstrate that supplementing the maternal diet with choline during pregnancy produces life-long cognitive benefits for the offspring. In contrast, the two experimental studies examining cognitive effects of maternal choline supplementation in humans produced inconsistent results, perhaps because of poor participant adherence and/or uncontrolled variation in intake of choline or other nutrients. We examined the effects of maternal choline supplementation during pregnancy on infant cognition, with intake of choline and other nutrients tightly controlled. Women entering their third trimester were randomized to consume, until delivery, either 480 mg choline/d (n = 13) or 930 mg choline/d (n = 13). Infant information processing speed and visuospatial memory were tested at 4, 7, 10, and 13 mo of age (n = 24). Mean reaction time averaged across the four ages was significantly faster for infants born to mothers in the 930 (vs. 480) mg choline/d group. This result indicates that maternal consumption of approximately twice the recommended amount of choline during the last trimester improves infant information processing speed. Furthermore, for the 480-mg choline/d group, there was a significant linear effect of exposure duration (infants exposed longer showed faster reaction times), suggesting that even modest increases in maternal choline intake during pregnancy may produce cognitive benefits for offspring.-Caudill, M. A., Strupp, B. J., Muscalu, L., Nevins, J. E. H., Canfield, R. L. Maternal choline supplementation during the third trimester of pregnancy improves infant information processing speed: a randomized, double-blind, controlled feeding study.

KEYWORDS: longitudinal; reaction time; saccade; visuospatial memory

Santamaria A, Di Benedetto A, Petrella E, Pintaudi B, Corrado F, D'Anna R, et al. Myo-inositol may prevent gestational diabetes onset in overweight women: a randomized, controlled trial. J Matern Fetal Neonatal Med. 2016 Oct;29(19):3234-7. doi: 10.3109/14767058.2015.1121478.

Abstract

OBJECTIVE: To evaluate whether myo-inositol supplementation may reduce gestational diabetes mellitus (GDM) rate in overweight women.
METHODS: In an open-label, randomized trial, myo-inositol (2 g plus 200 μg folic acid twice a day) or placebo (200 μg folic acid twice a day) was administered from the first trimester to delivery in pregnant overweight non-obese women (pre-pregnancy body mass index ≥ 25 and < 30 kg/m(2)). The primary outcome was the incidence of GDM.
RESULTS: From January 2012 to December 2014, 220 pregnant women were randomized at two Italian University hospitals, 110 to myo-inositol and 110 to placebo. The incidence of GDM was significantly lower in the myo-inositol group compared to the placebo group (11.6% versus 27.4%, respectively, p = 0.004). Myo-inositol treatment was associated with

a 67% risk reduction of developing GDM (OR 0.33; 95% CI 0.15-0.70).
CONCLUSIONS: Myo-inositol supplementation, administered since early pregnancy, reduces GDM incidence in overweight non-obese women.
KEYWORDS: Body mass index; gestational diabetes; myo-inositol; obese; overweight

OMEGA-3 AND OMEGA-6 ESSENTIAL FATTY ACIDS

OVERVIEWS

Neuropsychiatric Disorders

Bae JH, Kim G. Systematic review and meta-analysis of omega-3-fatty acids in elderly patients with depression. Nutrition Research. 2018 Feb 1;50:1-9.

Abstract

One of the typical symptoms of a psychological crisis is depression, an increasing concern in the elderly population. Although omega-3-polyunsaturated fatty acids (PUFAs) are reported to be promising nutrients for treating depression, currently, there are no systematic reviews or meta-analyses of randomized control trials that provide critical evidence regarding the potential benefits of omega-3 fatty acids in elderly patients with depression. This analysis was conducted to provide evidence for the clinical application of omega-3 fatty acids in the treatment of depressive symptoms of elderly subjects older than 65 years. Seven databases were searched from their inception date until September 2016. Following this search, 6 studies were selected, which included 4605 patients (mean age, 76.97 years; male-female ratio=3752:853; mean dose of omega 3 intake, 1.3 g/d). These results were divided into 2 categories: well-being mental health group and depressive group. In the well-being mental health group, the Hedges g was 0.12 (95% confidence interval, -0.05 to 0.29), which indicated no significant effect of n-3 PUFA supplementation on depressed mood compared with placebo. In the depressive group, the pooled Hedges g was -0.94 (95% CI, -1.37 to -0.50]) for the random-effects model, which indicated a large effect of n-3 PUFA supplementation on those with depressed mood compared with placebo. Although this review shows that omega-3 fatty acids are effective in the treatment of elderly depressed patients, the benefits of omega-3 fatty acid supplementation were significant only in the elderly patients with mild to moderate depression.

KEYWORDS: Depression; Meta-analysis; Omega-3-fatty acids; Systematic review

Canhada S, Castro K, Perry IS, Luft VC. Omega-3 fatty acids' supplementation in Alzheimer's disease: A systematic review. Nutritional neuroscience. 2018 Sep 14;21(8):529-38.

Abstract

INTRODUCTION: Alzheimer's disease (AD) is a neurodegeneration disorder characterized by progressive impairments of memory, language, reasoning, and other cognitive functions.

Evidence suggests that omega-3 fatty acids may act as a possible protection factor in AD.
OBJECTIVE: To evaluate the results available in the literature involving omega-3 fatty acids supplementation and its effect on cognitive function in AD patients.
METHODS: A systematic review of MEDLINE (from PubMed), Excerpta Medica Database, and Cochrane Library databases was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Inclusion criteria consisted in original intervention studies, controlled by placebo, that assessed the impact of supplementation or dietary intake of omega-3 fatty acids on cognitive function, in humans with AD, without limitation for prime date of publication.
RESULTS: Initial search resulted in 361 articles. Seven studies fully met the inclusion criteria. Most studies did not find statistically significant results for the omega-3 fatty acids supplementation compared to placebo, and those who show some benefit do it only in a few cognitive assessment scales. However, the effects of omega-3 fatty acids appear to be most effectively demonstrated in patients with very mild AD.
CONCLUSION: The effects of omega-3 fatty acids supplementation in mild AD corroborate epidemiological observational studies showing that omega-3 fatty acids may be beneficial in disease onset, when there is slight impairment of brain function. Although some studies have shown changes in scales of cognitive function in more severe cases, they are not enough to support omega-3 fatty acids supplementation in the treatment of AD.
KEYWORDS: Alzheimer's disease; Cognition; Docosahexaenoic acid; Eicosapentaenoic acid; Neuroinflammation; Omega-3 fatty acids

Chang JP, Su KP, Mondelli V, Pariante CM. Omega-3 polyunsaturated fatty acids in youths with attention deficit hyperactivity disorder: a systematic review and meta-analysis of clinical trials and biological studies. Neuropsychopharmacology. 2018 Feb;43(3):534. doi: 10.1038/npp.2017.160. Epub 2017 Jul 25.

Abstract

The role of omega-3 polyunsaturated fatty acids (omega-3 or n-3 PUFAs) in the pathogenesis and treatment of children and adolescents with attention deficit hyperactivity disorder (ADHD) is unclear. A systematic review followed by meta-analysis was conducted on: (1) randomized controlled trials (RCTs) assessing the effects of n-3 PUFAs on clinical symptoms and cognition in children and adolescent with ADHD; and (2) case-control studies assessing the levels of n-3 PUFAs in blood and buccal tissues of children and adolescents with ADHD. In seven RCTs, totalling n=534 randomized youth with ADHD, n-3 PUFAs supplementation improves ADHD clinical symptom scores (g=0.38, p<0.0001); and in three RCTs, totalling n=214 randomized youth with ADHD, n-3 PUFAs supplementation improves cognitive measures associated with attention (g=1.09, p=0.001). Moreover, children and adolescents with ADHD have lower levels of DHA (seven studies, n=412, g=-0.76, p=0.0002), EPA (seven studies, n=468, g=-0.38, p=0.0008), and total n-3 PUFAs (six studies, n=396, g=-0.58, p=0.0001). In summary, there is evidence that n-3 PUFAs supplementation monotherapy improves clinical symptoms and cognitive performances in children and adolescents with ADHD, and that these youth have a deficiency in n-3 PUFAs

levels. Our findings provide further support to the rationale for using n-3 PUFAs as a treatment option for ADHD.

Cheng YS, Tseng PT, Chen YW, Stubbs B, Yang WC, Chen TY, Wu CK, Lin PY. Supplementation of omega 3 fatty acids may improve hyperactivity, lethargy, and stereotypy in children with autism spectrum disorders: A meta-analysis of randomized controlled trials. Neuropsychiatric disease and treatment. 2017;13:2531.

Abstract

AIM: Deficiency of omega 3 fatty acids may be linked to autism spectrum disorder (ASD). Evidence about the potential therapeutic effects of supplementation of omega 3 fatty acids is lacking in ASD patients.

METHODS: We searched major electronic databases from inception to June 21, 2017, for randomized clinical trials, which compared treatment outcomes between supplementation of omega 3 fatty acids and placebo in patients with ASD. An exploratory random-effects meta-analysis of the included studies was undertaken.

RESULTS AND CONCLUSION: Six trials were included (n=194). Meta-analysis showed that supplementation of omega 3 fatty acids improved hyperactivity (difference in means =-2.692, 95% confidence interval [CI] =-5.364 to -0.020, P=0.048, studies =4, n=109), lethargy (difference in means =-1.969, 95% CI =-3.566 to -0.372, P=0.016, studies =4, n=109), and stereotypy (difference in means =-1.071, 95% CI =-2.114 to -0.029, P=0.044, studies =4, n=109). No significant differences emerged between supplementation of omega 3 fatty acids and placebo in global assessment of functioning (n=169) or social responsiveness (n=97). Our preliminary meta-analysis suggests that supplementation of omega 3 fatty acids may improve hyperactivity, lethargy, and stereotypy in ASD patients. However, the number of studies was limited and the overall effects were small, precluding definitive conclusions. Future large-scale randomized clinical trials are needed to confirm or refute our findings.

Grosso G, Micek A, Marventano S, Castellano S, Mistretta A, Pajak A, Galvano F. Dietary n-3 PUFA, fish consumption and depression: A systematic review and meta-analysis of observational studies. Journal of affective disorders. 2016 Nov 15;205:269-81. doi: 10.1016/j.jad.2016.08.011. Epub 2016 Aug 16.

Abstract

BACKGROUND: Fish consumption and n-3 polyunsaturated fatty acids (PUFA) have been hypothesized to exert preventive effects toward depressive disorders, but findings are contrasting. We aimed to systematically review and perform meta-analysis of results from

observational studies exploring the association between fish, n-3 PUFA dietary intake, and depression.

METHODS: A search on the main bibliographic source of the observational studies up to August 2015 was performed. Random-effects models of the highest versus the lowest (reference) category of exposure and dose-response meta-analysis were performed.

RESULTS: A total of 31 studies including 255,076 individuals and over 20,000 cases of depression, were examined. Analysis of 21 datasets investigating relation between fish consumption and depression resulted in significant reduced risk (RR=0.78, 95% CI: 0.69, 0.89), with a linear dose-response despite with moderate heterogeneity. Pooled risk estimates of depression for extreme categories of both total n-3 PUFA and fish-derived n-3 PUFA [eicosapentaenoic acid (EPA)+docosahexaenoic acid (DHA)] resulted in decreased risk for the highest compared with the lowest intake (RR=0.78, 95% CI: 0.67, 0.92 and RR=0.82, 95% CI: 0.73, 0.92, respectively) and dose-response analysis revealed a J-shaped association with a peak decreased risk for 1.8g/d intake of n-3 PUFA (RR=0.30, 95% CI: 0.09, 0.98).

LIMITATION: Design of the studies included and confounding due to lack adjustment for certain variables may exist.

CONCLUSIONS: The present analysis supports the hypothesis that dietary n-3 PUFA intake are associated with lower risk of depression.

Grosso G, Pajak A, Marventano S, Castellano S, Galvano F, Bucolo C, Drago F, Caraci F. Role of omega-3 fatty acids in the treatment of depressive disorders: a comprehensive meta-analysis of randomized clinical trials. PloS one. 2014 May 7;9(5):e96905.

Abstract

BACKGROUND: Despite omega-3 polyunsaturated fatty acids (PUFA) supplementation in depressed patients have been suggested to improve depressive symptomatology, previous findings are not univocal.

OBJECTIVES: To conduct an updated meta-analysis of randomized controlled trials (RCTs) of omega-3 PUFA treatment of depressive disorders, taking into account the clinical differences among patients included in the studies.

METHODS: A search on MEDLINE, EMBASE, PsycInfo, and the Cochrane Database of RCTs using omega-3 PUFA on patients with depressive symptoms published up to August 2013 was performed. Standardized mean difference in clinical measure of depression severity was primary outcome. Type of omega-3 used (particularly eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) and omega-3 as mono- or adjuvant therapy was also examined. Meta-regression analyses assessed the effects of study size, baseline depression severity, trial duration, dose of omega-3, and age of patients.

RESULTS: Meta-analysis of 11 and 8 trials conducted respectively on patients with a DSM-defined diagnosis of major depressive disorder (MDD) and patients with depressive symptomatology but no diagnosis of MDD demonstrated significant clinical benefit of omega-3 PUFA treatment compared to placebo (standardized difference in random-effects model 0.56 SD [95% CI: 0.20, 0.92] and 0.22 SD [95% CI: 0.01, 0.43], respectively; pooled

analysis was 0.38 SD [95% CI: 0.18, 0.59]). Use of mainly EPA within the preparation, rather than DHA, influenced final clinical efficacy. Significant clinical efficacy had the use of omega-3 PUFA as adjuvant rather than mono-therapy. No relation between efficacy and study size, baseline depression severity, trial duration, age of patients, and study quality was found. Omega-3 PUFA resulted effective in RCTs on patients with bipolar disorder, whereas no evidence was found for those exploring their efficacy on depressive symptoms in young populations, perinatal depression, primary disease other than depression and healthy subjects.
CONCLUSIONS: The use of omega-3 PUFA is effective in patients with diagnosis of MDD and on depressive patients without diagnosis of MDD.

Liu Wei-Hong, Zhang Cheng-Gui, Gao Peng-Fei, Liu Heng, Yang Jian-Fang. Omega-3 Fatty acids as Monotherapy in Treating Depression in Pregnant Women: A Meta- Analysis of Randomized Controlled Trials. Iranian Journal of Pharmaceutical Research. 2017 Sep;16(4):1593–9.

Abstract

Previous studies have reported inconsistent findings regarding the efficacy of omega-3 fatty acids on pregnant women with major depressive disorder (MDD). This meta-analysis was conducted to systematically evaluate the clinical applicability of omega-3 fatty acids in treating depression in pregnant women. Randomized controlled trials (RCTs) that compared omega-3 fatty acids to placebo for short-course treatment of depression in pregnant women were systematically reviewed between March 1999 and April 2015. The search terms used were 'depression', 'omega-3 fatty acids', 'fish oil', 'eicosapentaenoic acid' and 'docosahexaenoic acid'. Standardized difference in means of depression scale was used as the main outcome. Random effect model was used. The effects of baseline depression scores were studying by meta-regression analysis. patients received omega-3 fatty acids. The pooled standardized difference in means was 0.75 with 95% CI= (0.47, 1.04). The baseline depression scores had no effect on the efficacy. None of the recruited patients was withdrawn.

Mazahery H, Stonehouse W, Delshad M, Kruger M, Conlon C, Beck K, von Hurst P. Relationship between long chain n-3 polyunsaturated fatty acids and autism spectrum disorder: systematic review and meta-analysis of case-control and randomised controlled trials. Nutrients. 2017 Feb;9(2):155.

Abstract

Omega-3 long chain polyunsaturated fatty acid supplementation (*n*-3 LCPUFA) for treatment of Autism Spectrum Disorder (ASD) is popular. The results of previous systematic reviews and meta-analyses of *n*-3 LCPUFA supplementation on ASD outcomes were inconclusive. Two meta-analyses were conducted; meta-analysis 1 compared blood levels of LCPUFA and their ratios arachidonic acid (ARA) to docosahexaenoic acid (DHA),

ARA to eicosapentaenoic acid (EPA), or total *n*-6 to total *n*-3 LCPUFA in ASD to those of typically developing individuals (with no neurodevelopmental disorders), and meta-analysis 2 compared the effects of *n*-3 LCPUFA supplementation to placebo on symptoms of ASD. Case-control studies and randomised controlled trials (RCTs) were identified searching electronic databases up to May, 2016. Mean differences were pooled and analysed using inverse variance models. Heterogeneity was assessed using I^2 statistic. Fifteen case-control studies (n = 1193) were reviewed. Compared with typically developed, ASD populations had lower DHA (-2.14 [95% CI -3.22 to -1.07]; $p < 0.0001$; I^2 = 97%), EPA (-0.72 [95% CI -1.25 to -0.18]; $p = 0.008$; I^2 = 88%), and ARA (-0.83 [95% CI, -1.48 to -0.17]; $p = 0.01$; I^2 = 96%) and higher total *n*-6 LCPUFA to *n*-3 LCPUFA ratio (0.42 [95% CI 0.06 to 0.78]; $p = 0.02$; I^2 = 74%). Four RCTs were included in meta-analysis 2 (n = 107). Compared with placebo, *n*-3 LCPUFA improved social interaction (-1.96 [95% CI -3.5 to -0.34]; $p = 0.02$; $I^2 = 0$) and repetitive and restricted interests and behaviours (-1.08 [95% CI -2.17 to -0.01]; $p = 0.05$; $I^2 = 0$). Populations with ASD have lower *n*-3 LCPUFA status and *n*-3 LCPUFA supplementation can potentially improve some ASD symptoms. Further research with large sample size and adequate study duration is warranted to confirm the efficacy of *n*-3 LCPUFA.

Mocking RJ, Harmsen I, Assies J, Koeter MW, Ruhé H, Schene AH. Meta-analysis and meta-regression of omega-3 polyunsaturated fatty acid supplementation for major depressive disorder. Translational psychiatry. 2016 Mar;6(3):e756. doi: 10.1038/tp.2016.29

Abstract

Omega-3 polyunsaturated fatty acid (PUFA) supplementation has been proposed as (adjuvant) treatment for major depressive disorder (MDD). In the present meta-analysis, we pooled randomized placebo-controlled trials assessing the effects of omega-3 PUFA supplementation on depressive symptoms in MDD. Moreover, we performed meta-regression to test whether supplementation effects depended on eicosapentaenoic acid (EPA) or docosahexaenoic acid dose, their ratio, study duration, participants' age, percentage antidepressant users, baseline MDD symptom severity, publication year and study quality. To limit heterogeneity, we only included studies in adult patients with MDD assessed using standardized clinical interviews, and excluded studies that specifically studied perinatal/perimenopausal or comorbid MDD. Our PubMED/EMBASE search resulted in 1955 articles, from which we included 13 studies providing 1233 participants. After taking potential publication bias into account, meta-analysis showed an overall beneficial effect of omega-3 PUFAs on depressive symptoms in MDD (standardized mean difference=0.398 (0.114-0.682), P=0.006, random-effects model). As an explanation for significant heterogeneity (I(2)=73.36, P<0.001), meta-regression showed that higher EPA dose (β=0.00037 (0.00009-0.00065), P=0.009), higher percentage antidepressant users (β=0.0058 (0.00017-0.01144), P=0.044) and earlier publication year (β=-0.0735 (-0.143 to 0.004), P=0.04) were significantly associated with better outcome for PUFA supplementation. Additional sensitivity analyses were performed. In conclusion, present meta-analysis suggested a beneficial overall effect of omega-3 PUFA supplementation in MDD patients, especially for higher doses of EPA and in participants taking antidepressants. Future precision medicine trials should establish whether possible

interactions between EPA and antidepressants could provide targets to improve antidepressant response and its prediction. Furthermore, potential long-term biochemical side effects of high-dosed add-on EPA supplementation should be carefully monitored.

Yuhua Liao, Bo Xie, Huimin Zhang, Qian He, Lan Guo, M. Subramaniapillai, et al. Efficacy of omega-3 PUFAs in depression: A meta-analysis. Translational Psychiatry [Internet]. 2019 [cited 2019 Sep 19];(1):1.

Abstract

We conducted this meta-analysis of double-blind randomized placebo-controlled trials to estimate the efficacy of omega-3 polyunsaturated fatty acids (PUFAs), especially docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), in the improvement of depression. We applied a systematic bibliographic search in PubMed and EMBASE for articles published prior to 20 December 2017. This meta-analysis was performed using RevMan 5.3 and R 3.4.3, and means and standard deviations were calculated in fixed- or random-effects models based on the results of the Q-test. A sensitivity analysis was also conducted to evaluate the stability of the results, and publication bias was evaluated by a funnel plot and Egger's linear regression analysis. Our search resulted in 180 articles; we analyzed 26 studies, which included 2160 participants. The meta-analysis showed an overall beneficial effect of omega-3 polyunsaturated fatty acids on depression symptoms (SMD = -0.28, P = 0.004). Compared with placebo, EPA-pure (=100% EPA) and EPA-major formulations (≥60% EPA) demonstrated clinical benefits with an EPA dosage ≤1 g/d (SMD = -0.50, P = 0.003, and SMD = -1.03, P = 0.03, respectively), whereas DHA-pure and DHA-major formulations did not exhibit such benefits. Current evidence supports the finding that omega-3 PUFAs with EPA ≥ 60% at a dosage of ≤1 g/d would have beneficial effects on depression. Further studies are warranted to examine supplementation with omega-3 PUFAs for specific subgroups of subjects with inflammation, severity of depression, and the dose response for both EPA and DHA supplementation.

Cardiometabolic Disease and Risk

AbuMweis S, Jew S, Tayyem R, Agraib L. Eicosapentaenoic acid and docosahexaenoic acid containing supplements modulate risk factors for cardiovascular disease: a meta-analysis of randomised placebo-control human clinical trials. Journal of human nutrition and dietetics. 2018 Feb;31(1):67-84.

Abstract

BACKGROUND: Over 200 clinical trials have examined the effect of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) supplements on risk factors associated with cardiovascular disease. However, an updated analysis of the evidence is lacking. The aim of the present meta-analysis was to quantify the effect of supplements containing EPA and

DHA on risk factors for cardiovascular disease.
METHODS: An analysis was carried on 171 clinical trials with acceptable quality (Jadad score ≥3) that were identified from a comprehensive electronic search strategy of two databases (Pubmed and Cochrane Library). A random effect model was used to obtain an overall estimate on outcomes of interest. Heterogeneity between trial results was tested for using a standard chi-squared test.
RESULTS: Compared with control, EPA and DHA supplements produced significant reductions of triglycerides of 0.368 mmol L-1 [95% confidence interval (CI) = -0.427 to -0.309], systolic blood pressure of 2.195 mmHg (95% CI = -3.172 to -1.217), diastolic blood pressure of 1.08 mmHg (95% CI = -1.716 to -0.444), heart rate of 1.37 bpm (95% CI = -2.41 to -0.325) and C-reactive protein of 0.343 mg L-1 (95% CI = -0.454 to -0.232). This analysis indicates an increase in both low-density lipoprotein cholesterol (mean difference = 0.150 mmol L-1 ; 95% CI = 0.058-0.243) and high-density lipoprotein cholesterol (mean difference = 0.039 mmol L-1 ; 95% CI = 0.024-0.054). The triglyceride-lowering effect was dose-dependent.
CONCLUSIONS: The lipid-lowering, hypotensive, anti-arrhythmic and anti-inflammatory actions of EPA and DHA supplements were confirmed in this analysis of randomised placebo-control blinded clinical trials.

Farimani AR, Hariri M, Azimi-Nezhad M, Borji A, Zarei S, Hooshmand E. The effect of n-3 PUFAs on circulating adiponectin and leptin in patients with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. Acta Diabetologica [Internet]. 2018 Jul [cited 2019 Sep 19];55(7):641–52.

Abstract

AIM: N-3 PUFAs can potentially influence levels of inflammatory and non-inflammatory adipokines. Given the contradictory effects of n-3 PUFAs on serum levels of adipokines in type 2 diabetes, we conducted a systematic review and meta-analysis study of randomized placebo-controlled clinical trials that examined the effects of n-3 PUFAs on serum levels of leptin and adiponectin in patients with type 2 diabetes.

METHODS: The electronic databases, without regard to language restrictions including PubMed/Medline, Google Scholar, SCOPUS and ISI Web of Science until August 2017, were used to identify randomized controlled trials that assessed the effect of n-3 PUFAs on serum leptin and adiponectin concentrations in type 2 diabetes. Outcomes were extracted based on the mean ± SD as effect size at baseline and end of the intervention. Between-study heterogeneity was evaluated by the I^2 estimates and their 95% CIs. Funnel plot asymmetry was used to investigate the existence of publication bias. Stata software and Review Manager were used for statistical data analysis.

RESULTS: Data from 10 eligible articles involved 494 subjects with type 2 diabetes mellitus (intervention groups = 254 and control groups = 240), with age between 44 and 70 years, treated with doses of 0.52-7.4 g/day n-3 PUFAs. Adiponectin concentration

nonsignificantly increased by a MD = 0.17 µg/mL (95% CI - 0.11, 0.44). Also, leptin concentration nonsignificantly reduced by a MD = - 0.31 ng/mL (95% CI - 0.69, 0.07).

CONCLUSION: Plant and marine sources of n-3 PUFAs can modify serum leptin and adiponectin levels by increasing adiponectin and decreasing leptin levels in patients with type 2 diabetes. Due to some limitations in this study, further studies are needed to reach a definitive conclusion about the effect of n-3 PUFAs on the levels of leptin and adiponectin in T2DM.

Gao H, Geng T, Huang T, Zhao Q. Fish oil supplementation and insulin sensitivity: a systematic review and meta-analysis. Lipids in health and disease. 2017 Dec;16(1):131. doi: 10.1186/s12944-017-0528-0.

Abstract

BACKGROUND: Fish oil supplementation has been shown to be associated with a lower risk of metabolic syndrome and benefit a wide range of chronic diseases, such as cardiovascular disease, type 2 diabetes and several types of cancers. However, the evidence of fish oil supplementation on glucose metabolism and insulin sensitivity is still controversial. This meta-analysis summarized the exist evidence of the relationship between fish oil supplementation and insulin sensitivity and aimed to evaluate whether fish oil supplementation could improve insulin sensitivity.

METHODS: We searched the Cochrane Library, PubMed, Embase database for the relevant studies update to Dec 2016. Two researchers screened the literature independently by the selection and exclusion criteria. Studies were pooled using random effect models to estimate a pooled SMD and corresponding 95% CI. This meta-analysis was performed by Stata 13.1 software.

RESULTS: A total of 17 studies with 672 participants were included in this meta-analysis study after screening from 498 published articles found after the initial search. In a pooled analysis, fish oil supplementation had no effects on insulin sensitivity compared with the placebo (SMD 0.17, 95%CI -0.15 to 0.48, p = 0.292). In subgroup analysis, fish oil supplementation could benefit insulin sensitivity among people who were experiencing at least one symptom of metabolic disorders (SMD 0.53, 95% CI 0.17 to 0.88, p < 0.001). Similarly, there were no significant differences between subgroups of methods of insulin sensitivity, doses of omega-3polyunsaturated fatty acids (n-3 PUFA) of fish oil supplementation or duration of the intervention. The sensitivity analysis indicated that the results were robust.

CONCLUSIONS: Short-term fish oil supplementation is associated with increasing the insulin sensitivity among those people with metabolic disorders.

Guo X-F, Li K-L, Li J-M, Li D. Effects of EPA and DHA on blood pressure and inflammatory factors: a meta-analysis of randomized controlled trials. Critical Reviews In Food Science And Nutrition. 2019 Feb 4;1–14.

Abstract

The present study aimed to clarify whether eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have differential effects on blood pressure and inflammatory mediators. A systematic literature search was conducted in PubMed and Scopus updated to Apr. 2018. The mean changes in risk factors of chronic diseases were calculated as weighted mean difference (WMD) by using a random-effects model. Twenty randomized controlled trials (RCTs) were included. The summary estimate showed that EPA intervention significantly reduced systolic blood pressure (SBP) (-2.6 mmHg; 95%confident interval (CI): -4.6, -0.5 mmHg), especially in subjects with dyslipidemia (-3.8 mmHg; 95%CI: -6.7, -0.8 mmHg). The pooled effect indicated that supplemental DHA exerted a significant reduction in diastolic blood pressure (DBP) in subjects with dyslipidemia (-3.1 mmHg; 95%CI: -5.9, -0.2 mmHg). Both EPA (-0.56 mg/L; 95%CI: -1.13, 0.00) and DHA (-0.5 mg/L; 95%CI: -1.0, -0.03) significantly reduced the concentrations of C-reactive protein (CRP), respectively, especially in subjects with dyslipidemia and higher baseline CRP concentrations. Given that limited trials have focused on EPA or DHA intervention on concentrations of interleukin (IL)-6 and tumor necrosis factor (TNF)-α, further RCTs should be explored on these inflammatory factors. The present meta-analysis provides substantial evidence that EPA and DHA have independent (blood pressure) and shared (CRP concentration) effects on risk factors of chronic diseases, and high-quality RCTs with multi-center and large simple-size should be performed to confirm the present findings.

Innes J, Calder P. The differential effects of eicosapentaenoic acid and docosahexaenoic acid on cardiometabolic risk factors: a systematic review. International journal of molecular sciences. 2018 Feb;19(2):532.

Abstract

A large body of evidence supports the cardioprotective effects of the long-chain omega-3 polyunsaturated fatty acids (PUFAs), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). There is increasing interest in the independent effects of EPA and DHA in the modulation of cardiometabolic risk factors. This systematic review aims to appraise the latest available evidence of the differential effects of EPA and DHA on such risk factors. A systematic literature review was conducted up to May 2017. Randomised controlled trials were included if they met strict eligibility criteria, including EPA or DHA > 2 g/day and purity ≥ 90%. Eighteen identified articles were included, corresponding to six unique studies involving 527 participants. Both EPA and DHA lowered triglyceride concentration, with DHA having a greater triglyceride-lowering effect. Whilst total cholesterol levels were largely unchanged by EPA and DHA, DHA increased high-density lipoprotein (HDL) cholesterol concentration, particularly HDL_2, and increased low-density lipoprotein (LDL) cholesterol concentration and LDL particle size. Both EPA and DHA inhibited platelet activity, whilst DHA improved vascular function and lowered heart rate and blood pressure to a greater extent than EPA. The effects of EPA and DHA on inflammatory markers and glycaemic control were inconclusive; however both lowered oxidative stress. Thus, EPA

and DHA appear to have differential effects on cardiometabolic risk factors, but these need to be confirmed by larger clinical studies.

Jang H, Park K. Omega-3 and omega-6 polyunsaturated fatty acids and metabolic syndrome: A systematic review and meta-analysis. Clinical Nutrition. 2019 Jan 1

Abstract

BACKGROUND & AIMS: Previous studies suggest that polyunsaturated fatty acids (PUFAs) may reduce the risk of metabolic diseases, but some have shown ambiguous results. The aim of this study was to systematically evaluate and summarize available evidence on the association between omega-3 and omega-6 PUFA levels and risk of metabolic syndrome (MetS).
METHODS: A systematic literature search of articles published until December 2017 was conducted in PubMed, Web of Science, and Cochrane Library databases. Meta-analyses of the highest vs. lowest categories of omega-3 and omega-6 PUFAs were conducted using the random effects models.
RESULTS: Thirteen studies (2 case-control, 9 cross-sectional, 1 nested case-control, and 1 prospective cohort) with 36,542 individuals were included. Higher omega-3 PUFA levels in diets or blood were associated with a 26% reduction in the risk of MetS (odds ratio (OR)/relative risk (RR) 0.74, 95% confidence interval (CI) 0.62-0.89). This inverse association was evident among studies with Asian populations (OR/RR 0.69, 95% CI 0.54-0.87), but not among those with American/European populations (OR/RR 0.84, 95% CI 0.55-1.28). Null results were found regarding the association between circulating/dietary omega-6 PUFAs and MetS.
CONCLUSION: The present meta-analysis indicates that higher intakes of omega-3 PUFAs, but not omega-6 PUFAs, was associated with lower MetS risk; adding to the current body of evidence on the metabolic health effects of circulating/dietary omega-3 PUFAs.

KEYWORDS: Meta-analysis; Metabolic syndrome; Omega fatty acid; Polyunsaturated fatty acid; Systematic review

Leslie MA, Cohen DJ, Liddle DM, Robinson LE, Ma DW. A review of the effect of omega-3 polyunsaturated fatty acids on blood triacylglycerol levels in normolipidemic and borderline hyperlipidemic individuals. Lipids in health and disease. 2015 Dec;14(1):53.

Abstract

Circulating levels of triacylglycerol (TG) is a recognized risk factor for developing cardiovascular disease, a leading cause of death worldwide. The Institute of Medicine and the American Heart Association both recommend the consumption of n-3 polyunsaturated fatty acids (PUFA), specifically eicosapentaenoic acid (EPA) and docosahexaenoic acid

(DHA), to reduce serum TG in hyperlipidemic individuals. Additionally, a number of systematic reviews have shown that individuals with any degree of dyslipidemia, elevated serum TG and/or cholesterol, may benefit from a 20-30% reduction in serum TG after consuming n-3 PUFA derived from marine sources. Given that individuals with serum lipid levels ranging from healthy to borderline dyslipidemic constitute a large portion of the population, the focus of this review was to assess the potential for n-3 PUFA consumption to reduce serum TG in such individuals. A total of 1341 studies were retrieved and 38 clinical intervention studies, assessing 2270 individuals, were identified for inclusion in the current review. In summary, a 9-26% reduction in circulating TG was demonstrated in studies where ≥ 4 g/day of n-3 PUFA were consumed from either marine or EPA/DHA-enriched food sources, while a 4-51% reduction was found in studies where 1-5 g/day of EPA and/or DHA was consumed through supplements. Overall, this review summarizes the current evidence with regards to the beneficial effect of n-3 PUFA on circulating TG levels in normolipidemic to borderline hyperlipidemic, otherwise healthy, individuals. Thus demonstrating that n-3 PUFA may play an important role in the maintenance of cardiovascular health and disease prevention.

Mehdi Bahreini, Amir-Hossein Ramezani, Farideh Shishehbor, Anahita Mansoori. The effect of omega-3 on circulating adiponectin in adults with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. Canadian Journal of Diabetes [Internet]. 2018 Oct 1 [cited 2019 Sep 19];42(5):553–9.

Abstract

Whether consumption of omega-3 affects circulating adiponectin has not been established. The objective of this study was to evaluate the effect of omega-3 (food or supplement) on circulating adiponectin in patients with type 2 diabetes through a systematic review of meta-analyses of randomized controlled trials. PubMed, Scopus and Web of Science were searched for relevant studies through May 2016. Two researchers screened and abstracted the literature independently. Pooled estimates were obtained using the random-effects models. Overall, omega-3 increased adiponectin by 0.57 μg/mL (95% confidence interval [CI] 0.15 to 1.31; p=0.01, I-square=74.2% p for heterogeneity <0.001). The source of observed heterogeneity was explored by subgroup analyses. In subgroup analyses, adiponectin levels increased only in those who had consumed omega-3 for more than 8 weeks. This systematic review and meta-analysis of randomized, placebo-controlled clinical trials suggests that omega-3 in patients with type 2 diabetes increases circulating adiponectin. These findings support the potentially beneficial effects of dietary omega-3 in patients with type 2 diabetes on pathways related to adiponectin metabolism.

Miller E, Van Elswyk M, Alexander D. Long-chain omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid and blood pressure: a meta-analysis of randomized controlled trials. 2014;27(7):885-896.

Abstract

BACKGROUND: Although a large body of literature has been devoted to examining the relationship between eicosapentaenoic and docosahexaenoic acids (EPA+DHA) and blood pressure, past systematic reviews have been hampered by narrow inclusion criteria and a limited scope of analytical subgroups. In addition, no meta-analysis to date has captured the substantial volume of randomized controlled trials (RCTs) published in the past 2 years. The objective of this meta-analysis was to examine the effect of EPA+DHA, without upper dose limits and including food sources, on blood pressure in RCTs.
METHODS: Random-effects meta-analyses were used to generate weighted group mean differences and 95% confidence intervals (CIs) between the EPA+DHA group and the placebo group. Analyses were conducted for subgroups defined by key subject or study characteristics.
RESULTS: Seventy RCTs were included. Compared with placebo, EPA+DHA provision reduced systolic blood pressure (-1.52 mm Hg; 95% confidence interval (CI) = -2.25 to -0.79) and diastolic blood pressure (-0.99 mm Hg; 95% CI = -1.54 to -0.44) in the meta-analyses of all studies combined. The strongest effects of EPA+DHA were observed among untreated hypertensive subjects (systolic blood pressure = -4.51 mm Hg, 95% CI = -6.12 to -2.83; diastolic blood pressure = -3.05 mm Hg, 95% CI = -4.35 to - 1.74), although blood pressure also was lowered among normotensive subjects (systolic blood pressure = -1.25 mm Hg, 95% CI = -2.05 to -0.46; diastolic blood pressure = -0.62 mm Hg, 95% CI = -1.22 to -0.02).
CONCLUSIONS: Overall, available evidence from RCTs indicates that provision of EPA+DHA reduces systolic blood pressure, while provision of ≥2 grams reduces diastolic blood pressure.

O'Mahoney LL, Matu J, Price OJ, Birch KM, Ajjan RA, Farrar D, Tapp R, West DJ, Deighton K, Campbell MD. Omega-3 polyunsaturated fatty acids favourably modulate cardiometabolic biomarkers in type 2 diabetes: a meta-analysis and meta-regression of randomized controlled trials. Cardiovascular diabetology. 2018 Dec;17(1):98.

Abstract

BACKGROUND: Randomized controlled trials (RCTs) suggest that supplementation with omega-3polyunsaturated fatty acids (n-3PUFAs) may favourably modify cardiometabolic biomarkers in type 2 diabetes (T2DM). Previous meta-analyses are limited by insufficient sample sizes and omission of meta-regression techniques, and a large number of RCTs have subsequently been published since the last comprehensive meta-analysis. Updated information regarding the impact of dosage, duration or an interaction between these two factors is therefore warranted. The objective was to comprehensively assess the effect of n-3PUFAs supplementation on cardiometabolic biomarkers including lipid profiles, inflammatory parameters, blood pressure, and indices of glycaemic control, in

people with T2DM, and identify whether treatment dosage, duration or an interaction thereof modify these effects.

METHODS: Databases including PubMed and MEDLINE were searched until 13th July 2017 for RCTs investigating the effect of n-3PUFAs supplementation on lipid profiles, inflammatory parameters, blood pressure, and indices of glycaemic control. Data were pooled using random-effects meta-analysis and presented as standardised mean difference (Hedges g) with 95% confidence intervals (95% CI). Meta-regression analysis was performed to investigate the effects of duration of supplementation and total dosage of n-3PUFAs as moderator variables where appropriate.

RESULTS: A total of 45 RCTs were identified, involving 2674 people with T2DM. n-3PUFAs supplementation was associated with significant reductions in LDL [ES: - 0.10, (95% CI - 0.17, - 0.03); p = 0.007], VLDL (ES: - 0.26 (- 0.51, - 0.01); p = 0.044], triglycerides (ES: - 0.39 (- 0.55, - 0.24; p ≤ 0.001] and HbA1c (ES: - 0.27 (- 0.48, - 0.06); p = 0.010]. Moreover, n-3PUFAs supplementation was associated with reduction in plasma levels of TNF-α [ES: - 0.59 (- 1.17, - 0.01); p = 0.045] and IL-6 (ES: - 1.67 (- 3.14, - 0.20); p = 0.026]. All other lipid markers, indices of glycaemic control, inflammatory parameters, and blood pressure remained unchanged (p > 0.05).

CONCLUSIONS: n-3PUFAs supplementation produces favourable hypolipidemic effects, a reduction in pro-inflammatory cytokine levels and improvement in glycaemia. Neither duration nor dosage appear to explain the observed heterogeneity in response to n-3PUFAs. Trial registration This trial was registered at http://www.crd.york.ac.uk as CRD42016050802.

KEYWORDS: Cardiovascular disease; Docosahexaenoic acid; Eicosapentaenoic acid; Meta-analysis; Omega-3polyunsaturated fatty acids; Type 2 diabetes

Rangel-Huerta OD, Gil A. Omega 3 fatty acids in cardiovascular disease risk factors: an updated systematic review of randomised clinical trials. Clinical Nutrition. 2018 Feb 1;37(1):72-7.

Abstract

Several studies and reviews regarding the supplementation of omega-3 LC-PUFAs have been developed during the last years. Indeed, the evidence states that high doses omega-3 LC-PUFAs produce a small but significant decrease in blood pressure in older and hypertensive subjects. Due to the increasing interest in the benefits of LC-PUFAs, we aimed to evaluate the scientific evidence provided in the past five years (2012-2016) on the effects of the intake of omega-3 LC-PUFAs on cardiovascular risk factors such as inflammation and oxidative stress, through a systematic review in PubMed database. Twenty-eight articles were related to cardiovascular disease (CVD) and are included in this systematic review. The studies included healthy subjects and CVD patients; we included the number of subjects, type of study, type and doses of omega-3 LC-PUFAs, primary outcomes, and results. The use of omega-3 LC-PUFAs for ameliorating CVD risk factors can be recommended. However, the administration of omega-3 does not seem to show any benefit for the management of CVD or associated complications.

Tarik Becic, Christian Studenik. Effects of Omega-3 Supplementation on Adipocytokines in Prediabetes and Type 2 Diabetes Mellitus: Systematic Review and Meta-Analysis of Randomized Controlled Trials. Diabetes & Metabolism Journal. 2018;(2):101.

Abstract

BACKGROUND: The objective of this systematic review and meta-analysis was to determine the effects of omega-3 supplementation on adipocytokine levels in adult prediabetic and diabetic individuals.
METHODS: We searched PubMed, Medline, EMBASE, Scopus, Web of Science, Google Scholar, Cochrane Trial Register, World Health Organization Clinical Trial Registry Platform, and Clinicaltrial.gov Registry from inception to August 1, 2017 for randomized controlled trials. Pooled effects of interventions were assessed as mean difference using random effects model. We conducted a sensitivity, publication bias and subgroup analysis.
RESULTS: Fourteen studies individuals (n=685) were included in the meta-analysis. Omega-3 supplementation increased levels of adiponectin (0.48 µg/mL; 95% confidence interval [CI], 0.27 to 0.68; P<0.00001, n=10 trials), but effects disappeared after sensitivity analysis. Tumor necrosis factor α (TNF-α) levels were reduced (-1.71; 95% CI, -3.38 to -0.14; P=0.03, n=8 trials). Treatment duration shorter than 12 weeks was associated with greater reduction than longer treatment duration. Levels of other adipocytokines were not significantly affected. Publication bias could generally not be excluded.
CONCLUSION: Eicosapentaenoic acid and docosahexaenoic acid supplementation may increase adiponectin and reduce TNF-α levels in this population group. However, due to overall study heterogeneity and potential publication bias, a cautious interpretation is needed.

Zhang YY, Liu W, Zhao TY, Tian HM. Efficacy of omega-3 polyunsaturated fatty acids supplementation in managing overweight and obesity: a meta-analysis of randomized clinical trials. The journal of nutrition, health & aging. 2017 Feb 1;21(2):187-92.

Abstract

OBJECTIVE: Studies in rodents and humans have indicated that omega-3 polyunsaturated fatty acids (n-3 PUFA) may reduce weight. The aim of this meta-analysis was to evaluate evidence for the efficacy of n-3 PUFA in managing overweight and obesity.

METHODS: We performed a systematic search of PubMed, Embase, and Cochrane Central Register of Controlled Trials until May 2015. Two reviewers independently determined the eligibility of studies and assessed the reporting quality of included randomized controlled trials (RCTs).

RESULTS: A total of 11 RCTs involving 617 participants were included in this meta-analysis. Based on the meta-analysis of nine studies, a statistically nonsignificant difference was revealed in weight loss between n-3 PUFA and placebo (p=0.99; weighted mean difference [WMD]: 0.00; 95% confidence interval [CI] -0.42 to 0.43), whereas n-3 PUFA was superior to placebo in reducing serum triglyceride levels (p=0.0007; standard median difference [Std MD]: -

0.59; 95% CI -0.93 to -0.25). Based on meta-analysis of seven studies, the analysis of aggregated data showed a significant reduction in waist circumference (p=0.005; WMD: -0.53; 95% CI -0.90 to -0.16). There were no significant differences in body mass index, total serum levels of cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, and fasting glucose levels.

CONCLUSIONS: The evidence from RCTs showed that n-3 PUFA might effectively reduce waist circumference and triglyceride levels in overweight and obese adults, but n-3 PUFA may not effectively reduce body weight. Given the small number and poor quality of RCTs included in the meta-analysis, these results are inconclusive. A large-scale, well-designed RCT is needed to further address this issue.

KEYWORDS: C-recative protein; blood pressure; cardiovascular; docosahexaenoic acid; eicosapentaenoic acid; heart rate; inflammation; risk factors; triglycerides

Pregnancy

Gao L, Lin L, Shan N, Ren C-Y, Long X, Sun Y-H, et al. The impact of omega-3 fatty acid supplementation on glycemic control in patients with gestational diabetes: a systematic review and meta-analysis of randomized controlled studies. The Journal Of Maternal-Fetal & Neonatal Medicine: The Official Journal Of The European Association Of Perinatal Medicine, The Federation Of Asia And Oceania Perinatal Societies, The International Society Of Perinatal Obstetricians. 2018 Oct 29;1–7.

Abstract

BACKGROUND: Omega-3 fatty acid supplementation shows some treatment efficacy for gestational diabetes. This systematic review and meta-analysis is conducted to investigate the efficacy of omega-3 fatty acid supplementation for glycemic control in patients with gestational diabetes.

METHODS: The databases including PubMed, Embase, Web of science, EBSCO, and Cochrane Library databases are systematically searched for collecting the randomized controlled trials (RCTs) regarding the efficacy of omega-3 fatty acid versus placebo for gestational diabetes.

RESULTS: This meta-analysis has included seven RCTs. Compared with placebo group in patients with gestational diabetes, omega-3 fatty acids supplementation results in remarkably reduced fasting plasma glucose (FPG) (standard mean difference (std. MD) = -0.56; 95% confidence interval (CI) = -0.87 to -0.24; p = .0005), homeostatic model of assessment for insulin resistance (HOMA-IR) (std. MD = -0.52; 95% CI = -0.83 to -0.21; p = .001), but has no statistical impact on macrosomia (risk ratio (RR) = 0.48; 95% CI = 0.22-1.02; p = .06), newborns' hyperbilirubinemia (RR = 0.46; 95% CI = 0.19-1.10; p = .08), nitric oxide (NO) (std. MD = 0.17; 95% CI = -0.64-0.98; p = .68), preterm delivery (RR = 1.75; 95% CI = 0.08-3.80; p=.16) and preeclampsia (RR =0.74; 95% CI = 0.26-2.16; p = .59). However, notably decreased high sensitivity C-reactive protein (hs-CRP) is revealed after omega-3 fatty acids supplementation (std. MD = -1.14; 95% CI = -2.0 to -0.29; p = .009).

CONCLUSIONS: Omega-3 fatty acids supplementation can provide substantially beneficial

effects on glycemic control and inflammatory response for gestational diabetes.
KEYWORDS: Gestational diabetes; glycemic control; meta-analysis; omega-3 fatty acid; randomized controlled trials

Kar S, Wong M, Rogozinska E, Thangaratinam S. Effects of omega-3 fatty acids in prevention of early preterm delivery: a systematic review and meta-analysis of randomized studies. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2016 Mar 1;198:40-6. doi: 10.1016/j.ejogrb.2015.11.033. Epub 2015 Nov 30.

Abstract

OBJECTIVE: Preterm birth continues to be the one of the leading causes of infant deaths worldwide. There is a need for effective, easily available, safe and acceptable interventions to prevent preterm delivery, especially before 34 weeks of gestation. Omega-3 fatty acids such as EPA (eicosapentanoic acid) and DHA (docosahexanoic acid) are available as over the counter nutritional supplements, and are taken by women to improve pregnancy outcomes, without any clear recommendations. We undertook a systematic review to assess the effects of omega-3 fatty acids on early (<34 weeks) and any (<37 weeks) preterm delivery.
METHODS: We searched MEDLINE, EMBASE and Cochrane Library from inception to 2014 without any language restrictions. Study selection, quality assessment and data extraction were done by two independent reviewers. Results were summarized as relative risks and 95% confidence intervals for dichotomous outcomes and mean differences for continuous outcomes.
RESULTS: Of the nine included trials (5980 women), six (4193 women) evaluated the effects of omega-3 fatty acids on early preterm delivery. The risk of early preterm delivery was reduced by 58% (RR 0.42; 95% CI 0.27-0.66; I(2)=0%; p=0.0002) and any preterm delivery by 17% (RR 0.83; 95% CI 0.70-0.98; I(2)=0%; p=0.03) with the intervention. There was a significant increase in the mean gestational age by 1.95 weeks (95% CI 0.42-3.48 weeks; I(2)=0.47; p=0.01) and mean birth weight by 122.1g (95% CI 47.4-196.8; I(2)=0.84; p=0.001) in the intervention group compared to the controls. Subgroup analysis showed no significant differences in the effects between the groups according to the risk status, dose and timing of the intervention.
CONCLUSION: Omega-3 fatty acids are effective in preventing early and any preterm delivery. The intervention is simple and easily available and has the potential to influence population based strategies in the prevention of preterm birth.
KEYWORDS: Omega-3 fatty acid; Pregnancy; Preterm birth

Lin PY, Chang CH, Chong MF, Chen H, Su KP. Polyunsaturated fatty acids in perinatal depression: a systematic review and meta-analysis. Biological psychiatry. 2017 Oct 15;82(8):560-9.

Abstract

BACKGROUND: Omega-3 (or n-3) polyunsaturated fatty acids (PUFAs) are promising antidepressant treatments for perinatal depression (PND) because of supporting evidence from clinical trials, the advantage in safety, and their anti-inflammatory and neuroplastic effects. Although several observational studies have shown n-3 PUFA deficits in women with PND, the results of individual PUFAs from different studies were inconsistent.

METHODS: This systematic review and meta-analysis aims to compare the levels of PUFA indices, including eicosapentaenoic acid, docosahexaenoic acid, arachidonic acid, total n-3, total n-6, and the n-6/n-3 ratio between women with PND and healthy control subjects. The meta-analysis included 12 eligible studies available as of December 2016. The effect sizes were synthesized by using a random effects model. In addition, we performed subgroup analysis for the PUFA levels in patients with prenatal and postnatal depression, both of which were compared with healthy control subjects.

RESULTS: There were significantly lower levels of total n-3 PUFAs and docosahexaenoic acid and significantly increased n-6/n-3 ratios in PND patients. In the subgroup analyses, there were significantly lower levels of n-3 PUFAs, eicosapentaenoic acid, and docosahexaenoic acid in women with prenatal depression. The n-6/n-3 ratio was significantly increased in both prenatal and postnatal depression subgroups.

CONCLUSIONS: Our meta-analysis consolidates the important role of n-3 PUFAs in PND. Nutritional medicine is an important strategy to improve the effectiveness of treatment for depression, and our findings provide the strong rationale to conduct clinical trials to test the therapeutic and prophylactic effects of n-3 PUFAs in PND.

KEYWORDS: Arachidonic acid; Docosahexaenoic acid; Eicosapentaenoic acid; Omega-3; Perinatal depression; Polyunsaturated fatty acids

Middleton P, Gomersall JC, Gould JF, Shepherd E, Olsen SF, Makrides M. Omega-3 fatty acid addition during pregnancy. Cochrane Database of Systematic Reviews. 2018(11).

Abstract

BACKGROUND: Higher intakes of foods containing omega-3 long-chain polyunsaturated fatty acids (LCPUFA), such as fish, during pregnancy have been associated with longer gestations and improved perinatal outcomes. This is an update of a review that was first published in 2006.

OBJECTIVES: To assess the effects of omega-3 LCPUFA, as supplements or as dietary additions, during pregnancy on maternal, perinatal, and neonatal outcomes and longer-term outcomes for mother and child.

SEARCH METHODS: For this update, we searched Cochrane Pregnancy and Childbirth's Trials Register, ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP) (16 August 2018), and reference lists of retrieved studies.

SELECTION CRITERIA: Randomised controlled trials (RCTs) comparing omega-3 fatty acids (as supplements or as foods, stand-alone interventions, or with a co-intervention) during pregnancy with placebo or no omega-3, and studies or study arms directly comparing omega-3LCPUFA doses or types. Trials published in abstract form were eligible for inclusion.

DATA COLLECTION AND ANALYSIS: Two review authors independently assessed study

eligibility, extracted data, assessed risk of bias in trials and assessed quality of evidence for prespecified birth/infant, maternal, child/adult and health service outcomes using the GRADE approach.

MAIN RESULTS: In this update, we included 70 RCTs (involving 19,927 women at low, mixed or high risk of poor pregnancy outcomes) which compared omega-3 LCPUFA interventions (supplements and food) compared with placebo or no omega-3. Overall study-level risk of bias was mixed, with selection and performance bias mostly at low risk, but there was high risk of attrition bias in some trials. Most trials were conducted in upper-middle or high-income countries; and nearly half the trials included women at increased/high risk for factors which might increase the risk of adverse maternal and birth outcomes. Preterm birth < 37 weeks (13.4% versus 11.9%; risk ratio (RR) 0.89, 95% confidence interval (CI) 0.81 to 0.97; 26 RCTs, 10,304 participants; high-quality evidence) and early preterm birth < 34 weeks (4.6% versus 2.7%; RR 0.58, 95% CI 0.44 to 0.77; 9 RCTs, 5204 participants; high-quality evidence) were both lower in women who received omega-3LCPUFA compared with no omega-3. Prolonged gestation > 42 weeks was probably increased from 1.6% to 2.6% in women who received omega-3 LCPUFA compared with no omega-3 (RR 1.61 95% CI 1.11 to 2.33; 5141 participants; 6 RCTs; moderate-quality evidence).For infants, there was a possibly reduced risk of perinatal death (RR 0.75, 95% CI 0.54 to 1.03; 10 RCTs, 7416 participants; moderate-quality evidence: 62/3715 versus 83/3701 infants) and possibly fewer neonatal care admissions (RR 0.92, 95% CI 0.83 to 1.03; 9 RCTs, 6920 participants; moderate-quality evidence - 483/3475 infants versus 519/3445 infants). There was a reduced risk of low birthweight (LBW) babies (15.6% versus 14%; RR 0.90, 95% CI 0.82 to 0.99; 15 trials, 8449 participants; high-quality evidence); but a possible small increase in large-for-gestational age (LGA) babies (RR 1.15, 95% CI 0.97 to 1.36; 6 RCTs, 3722 participants; moderate-quality evidence, for omega-3LCPUFA compared with no omega-3. Little or no difference in small-for-gestational age or intrauterine growth restriction (RR 1.01, 95% CI 0.90 to 1.13; 8 RCTs, 6907 participants; moderate-quality evidence) was seen. For the maternal outcomes, there is insufficient evidence to determine the effects of omega-3 on induction post-term (average RR 0.82, 95% CI 0.22 to 2.98; 3 trials, 2900 participants; low-quality evidence), maternal serious adverse events (RR 1.04, 95% CI 0.40 to 2.72; 2 trials, 2690 participants; low-quality evidence), maternal admission to intensive care (RR 0.56, 95% CI 0.12 to 2.63; 2 trials, 2458 participants; low-quality evidence), or postnatal depression (average RR 0.99, 95% CI 0.56 to 1.77; 2 trials, 2431 participants; low-quality evidence). Mean gestational length was greater in women who received omega-3 LCPUFA (mean difference (MD) 1.67 days, 95% CI 0.95 to 2.39; 41 trials, 12,517 participants; moderate-quality evidence), and pre-eclampsia may possibly be reduced with omega-3 LCPUFA (RR 0.84, 95% CI 0.69 to 1.01; 20 trials, 8306 participants; low-quality evidence).For the child/adult outcomes, very few differences between antenatal omega-3 LCPUFA supplementation and no omega-3 were observed in cognition, IQ, vision, other neurodevelopment and growth outcomes, language and behaviour (mostly low-quality to very low-quality evidence). The effect of omega-3 LCPUFA on body mass index at 19 years (MD 0, 95% CI -0.83 to 0.83; 1 trial, 243 participants; very low-quality evidence) was uncertain. No data were reported for development of diabetes in the children of study participants.

AUTHORS' CONCLUSIONS: In the overall analysis, preterm birth < 37 weeks and early preterm birth < 34 weeks were reduced in women receiving omega-3 LCPUFA compared with no omega-3. There was a possibly reduced risk of perinatal death and of neonatal care

admission, a reduced risk of LBW babies; and possibly a small increased risk of LGA babies with omega-3 LCPUFA. For our GRADE quality assessments, we assessed most of the important perinatal outcomes as high-quality (e.g. preterm birth) or moderate-quality evidence (e.g. perinatal death). For the other outcome domains (maternal, child/adult and health service outcomes) GRADE ratings ranged from moderate to very low, with over half rated as low. Reasons for downgrading across the domain were mostly due to design limitations and imprecision. Omega-3 LCPUFA supplementation during pregnancy is an effective strategy for reducing the incidence of preterm birth, although it probably increases the incidence of post-term pregnancies. More studies comparing omega-3 LCPUFA and placebo (to establish causality in relation to preterm birth) are not needed at this stage. A further 23 ongoing trials are still to report on over 5000 women, so no more RCTs are needed that compare omega-3 LCPUFA against placebo or no intervention. However, further follow-up of completed trials is needed to assess longer-term outcomes for mother and child, to improve understanding of metabolic, growth and neurodevelopment pathways in particular, and to establish if, and how, outcomes vary by different types of omega-3 LCPUFA, timing and doses; or by characteristics of women.

Zhong N, Wang J. The efficacy of omega-3 fatty acid for gestational diabetes: a meta-analysis of randomized controlled trials. Gynecological Endocrinology: The Official Journal Of The International Society Of Gynecological Endocrinology. 2019 Jan;35(1):4–9.

Abstract

INTRODUCTION: The efficacy of omega-3 fatty acid to treat gestational diabetes remains controversial. We conduct a systematic review and meta-analysis to explore the influence of omega-3 fatty acid versus placebo on gestational diabetes.
METHODS: We search PubMed, EMbase, Web of science, EBSCO, and Cochrane library databases through March 2018 for randomized controlled trials (RCTs) assessing the effect of omega-3 fatty acid versus placebo on gestational diabetes. This meta-analysis is performed using the random-effect model.
RESULTS: Five RCTs are included in the meta-analysis. Overall, compared with control group for gestational diabetes, omega-3 fatty acid can significantly reduce fasting plasma glucose (FPG) (mean difference (MD) = -4.91; 95% confidence interval (CI) = -8.16 to -1.66; p = .003), homeostatic model of assessment for insulin resistance (HOMA-IR, MD = -0.99; 95% CI = -1.61 to -0.37; p = .002), high sensitivity C-reactive protein (hs-CRP, MD = -1.43; 95% CI = -2.54 to -0.31; p = .01), but has no remarkable influence on preterm delivery (RR = 1.61; 95% CI = 0.36-7.16; p = .53), gestational age (MD = 0.09; 95% CI = -0.01 to 0.20; p = .08), macrosomia (RR = 0.64; 95% CI = 0.26-1.62; p = .3), newborn weight (MD = 3.37; 95% CI = -15.75 to 22.50; p = .73), and 5-min Apgar score (MD = 0; 95% CI = -0.02 to 0.02; p = .92).
CONCLUSIONS: Omega-3 fatty acids is associated with significantly reduced FPG, HOMA-IR, and hs-CRP in patients with gestational diabetes.
KEYWORDS: Omega-3 fatty acid; fasting plasma glucose (FPG); gestational diabetes; glycemic control

Non-Alcoholic Fatty Liver Disease

Chen LH, Wang YF, Xu QH, Chen SS. Omega-3 fatty acids as a treatment for non-alcoholic fatty liver disease in children: A systematic review and meta-analysis of randomized controlled trials. Clinical Nutrition. 2018 Apr 1;37(2):516-21.

Abstract

BACKGROUND: The most typical chronic liver disease in children and adolescents is non-alcoholic fatty liver disease (NAFLD). The dietary addition of ω-3 polyunsaturated fatty acids (PUFAs) provides a promising therapy for children with NAFLD due to its convenience and safety; however, several studies suggested contradictory results for PUFA supplementation in children. Hence, we performed a systematic review and meta-analysis to evaluate the effectiveness of PUFA supplementation in children with NAFLD.
METHODS: Published randomized controlled trials (RCTs) that evaluated the effectiveness of the dietary addition of PUFA in children with NAFLD were considered. The primary result was the alteration in hepatic steatosis grade on ultrasound after treatment. The secondary outcomes included alanine aminotransferase (ALT), aspartate aminotransferase (AST), C-reactive protein (CRP) and components of metabolic syndrome. Predefined sensitivity analysis was also performed to explore possible explanations for heterogeneity in the evaluations.
RESULTS: In total, 4 studies with 263 subjects were identified. PUFA supplementation was associated with significantly improved hepatic steatosis grade on ultrasound (risk difference: 25%, 95% CI: 12-38%), without heterogeneity (P = 0.27, I2 = 24%). Sensitivity analysis confirmed the robustness of our findings. PUFA supplementation could decrease AST levels after 6 months, but could only reduce ALT levels after 12 months. PUFA did not have a significant effect on most components of metabolic syndrome and the CRP level.
CONCLUSION: ω-3 PUFA supplementation can improve liver steatosis and liver functions, and it is a potential food supplementation to treat NAFLD in children.

Guo XF, Yang B, Tang J, Li D. Fatty acid and non-alcoholic fatty liver disease: meta-analyses of case-control and randomized controlled trials. Clin Nutr. 2018 Feb;37(1):113-122. doi: 10.1016/j.clnu.2017.01.003.

Abstract

BACKGROUND AND AIMS: Blood and/or liver fatty acid contents of healthy subjects and non-alcoholic fatty liver disease (NAFLD) patients have shown inconsistent associations. In addition, the results of randomized controlled trials (RCTs) in relation to the effects of n-3 polyunsaturated fatty acid (PUFA) supplementation on alanine aminotransferase (ALT), aspartate aminotransferase (AST), liver fat, triglyceride (TAG) and fasting glucose levels are inconsistent. The present study aimed to investigate the differences of fatty acid content in the blood and/or liver tissue between healthy subjects and NAFLD patients, and to quantify the benefits of n-3 PUFA therapy in NAFLD patients.
METHODS: A systematic literature search was performed up to November 2016 using PubMed and Scopus databases. The differences of fatty acid content between cases and

controls were calculated as weighted mean differences (WMD) by using a random-effects model. The intervention effects of RCTs were calculated as WMD for net changes in ALT, AST, liver fat, TAG and fasting glucose levels, respectively. Meta-regression with restricted maximum likelihood estimation was used to evaluate a potential linear relationship between confounding factors and effect sizes. Generalized least square was performed for dose-response analysis.
RESULTS: Ten eligible case-control studies and 11 RCTs were included. The pooled estimates of case-control studies showed that blood and/or liver docosahexaenoic acid (DHA) content was significantly higher in the controls compared with cases. The pooled estimates of RCTs showed that n-3 PUFA supplementation significantly reduced the ALT (-7.53 U/L; 95% CI: -9.98, -5.08 U/L), ASL (-7.10 U/L, 95% CI: -11.67, -2.52 U/L) and TAG (-36.16 mg/dL, 95% CI: -49.15, -23.18 mg/dL) concentrations, and marginally reduced the liver fat content (-5.11%, 95% CI: -10.24, 0.02%, P = 0.051), but not fasting glucose. Dose-response analysis of RCTs showed that 1 g per day increment of eicosapentaenoic acid (EPA)+DHA was associated with a 3.14 U/L, 2.43 U/L, 2.74% and 9.97 mg/dL reduction in ALT (95% CI: -5.25, -1.02 U/L), AST (95% CI: -3.90, -0.90 U/L), liver fat (95% CI: -4.32, -1.16%) and TAG (95% CI: -14.47, -5.48 mg/dL) levels, respectively.

CONCLUSIONS: The present meta-analysis provides substantial evidence that n-3 PUFA supplementation, especially DHA, has a favorable effect in treatment of NAFLD.

Yan J-H, Guan B-J, Gao H-Y, Peng X-E. Omega-3 polyunsaturated fatty acid supplementation and non-alcoholic fatty liver disease A meta-analysis of randomized controlled trials. MEDICINE;97(37).

Abstract

BACKGROUND: Clinical trials examining the therapeutic benefit of omega-3 polyunsaturated fatty acids (ω-3 PUFAs) on non-alcoholic fatty liver disease (NAFLD) have reported inconsistent results. We performed a meta-analysis of randomized controlled trials (RCTs) examining the effect of ω-3 PUFA supplementation on NAFLD, and provide substantial evidence on whether ω-3 PUFA supplementation has a favorable effect for treating NAFLD.
METHODS: We searched the PubMed, Cochrane Library, Springer Link, China National Knowledge Infrastructure (CNKI), Wanfang, and Chinese Scientific and Technological Journal (VIP) databases for RCTs on oral ω-3 PUFA supplementation in patients with NAFLD. The data were pooled; meta-analyses were conducted using random-effect or fixed-effect models.
RESULTS: Eighteen studies involving 1424 patients were included. We found a significant benefit for ω-3 PUFAs vs control for liver fat, alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transferase, triglycerides, insulin resistance, and glucose. However, there was significant interstudy heterogeneity. Subgroup and regression analyses showed no significantly clear methodologic discrepancy. Publication bias and serious adverse events were not detected.
CONCLUSIONS: Our meta-analysis suggests that ω-3 PUFA supplementation may decrease liver fat and hepatic enzyme parameters. However, more large-scale, well-

designed RCTs are needed to confirm the effect of ω-3 PUFA supplementation on these parameters.

Yu L, Yuan M, Wang L. The effect of omega-3 unsaturated fatty acids on non-alcoholic fatty liver disease: A systematic review and meta-analysis of RCTs. Pakistan journal of medical sciences. 2017;33(4):1022-8.

Abstract

OBJECTIVE: During the treatment of diseases such as angiocardiopathy, blood lipid abnormalities and metabolic syndrome, omega-3unsaturated fatty acids (PUFA) can reduce plasma lipids and improve cardiovascular status, thus ameliorating disease severity. We aimed to explore the effects of PUFA supplementation in patients with non-alcoholic fatty liver disease (NAFLD).
METHODS: A systematic literature search was performed during March 2016 for randomized controlled trials using PUFA or fish oil supplementation in patients with NAFLD or non-alcoholic steatohepatitis (NASH). All Randomized controlled trials were retrieved from MEDLINE and EMBASE database up to date (March 2016). A meta-analysis of key outcomes (serum level of liver enzymes and lipids) were identified in these studies. The mean difference (MD) and the corresponding 95% confidence intervals (CIs) were used as measures of effect size.
RESULTS: Thirteen studies were included, consisting of 266 patients in the PUFA group and 402 cases in the control group. Serum level of alanine aminotransferase (ALT) was lower in the PUFA group than that in in the controls [MD=-9.18, 95% CI (-12.41, -5.96), P <0.00001]. However, PUFA treatment did not affect aspartate aminotransferase (AST) [MD=-5.07, 95% CI (-12.65, 2.51), P= 0.19], gamma-glutamyl transferase (GGT) [MD=-1.91, 95% CI (-4.15, 0.33), P <0.009].
CONCLUSIONS: PUFA supplementation may affects serum level of ALT and improve liver function in patients with NAFLD.

KEYWORDS: Meta-analysis; Non-alcoholic fatty liver disease; Omega-3 unsaturated fatty acids

Gastrointestinal Disorders

Mozaffari H, Daneshzad E, Larijani B, Bellissimo N, Azadbakht L. Dietary intake of fish, n-3 polyunsaturated fatty acids, and risk of inflammatory bowel disease: a systematic review and meta-analysis of observational studies. European Journal Of Nutrition. 2019 Jan 24

Abstract

PURPOSE: Fish consumption and dietary intake of n-3 polyunsaturated acids (PUFAs) may be associated with inflammatory bowel disease (IBD). We aimed to conduct a systematic review and summarize published articles on the association between fish consumption and dietary intake of n-3 PUFAs with the risk of IBD.

METHODS: PubMed, Scopus, and Web of Science databases were used to conduct a comprehensive search and identify eligible literature published prior to January 2019. Fixed-effects model or random-effects models (DerSimonian-Laird method) were applied to pool the effect sizes. Cochrane Q test was used to trace the potential source of heterogeneity across studies.
RESULTS: 12 studies (5 prospective and 7 case-control) were included in the systematic review, which ten of them were eligible for inclusion in the meta-analysis. Studies were included a total sample size of 282610 participants which 2002 of them were cases of IBD [1061 Crohn's disease (CD) and 937 ulcerative colitis (UC)]. A negative association was found between fish consumption and the incidence of CD (pooled effect size: 0.54, 95%CI: 0.31-0.96, P = 0.03). There was no relationship between total dietary n-3 PUFAs intake and IBD (pooled effect size: 1.17, 95%CI: 0.80-1.72, P = 0.41). A significant inverse association was observed between dietary long-chain n-3 PUFAs and the risk of UC (pooled effect size: 0.75, 95%CI: 0.57-0.98, P = 0.03). Moreover, no association was found between α-Linolenic acid (ALA) and IBD (pooled effect size: 1.17, 95%CI: 0.63-2.17, P = 0.62).
CONCLUSIONS: Findings showed a negative association between fish consumption and the risk of CD. Moreover, there was a significant inverse association between dietary long-chain n-3 PUFAs and the risk of UC.
KEYWORDS: Fish; Inflammatory bowel disease; Meta-analysis; Omega-3

Neurological Disorders and Pain Syndromes

Maghsoumi-Norouzabad L, Mansoori A, Abed R, Shishehbor F. Effects of omega-3 fatty acids on the frequency, severity, and duration of migraine attacks: a systematic review and meta-analysis of randomized controlled trials. Nutritional neuroscience. 2018 Oct 21;21(9):614-23. doi: 10.1080/1028415X.2017.1344371. Epub 2017 Jun 30.

Abstract

The present systematic review with meta-analysis of randomized controlled trials (RCTs) aimed to analyze the effectiveness of omega-3 fatty acids on the frequency, severity, and duration of migraine. This systematic review was performed by searching several databases for controlled clinical trials. Of the 13 trials, five, two, and three RCTs met the eligibility criteria to evaluate the efficacy of omega-3 on the frequency, duration, and severity of migraine attacks, respectively. The Jadad scale was used to evaluate the risk of bias analysis. Overall estimates of the intervention effect were obtained from random-effect meta-analysis. The studies' heterogeneity was evaluated using the chi-squared test (χ^2) (Cochran's test (Q test)) and I^2 Index. Potential sources of heterogeneity among the trials were investigated by meta-regression analyses. The results showed that omega-3 intake had no effect on frequency (WMD = -0.20; 95%CI -0.67, 0.27; P = 0.401, and I^2 = 4.6%; P = 0.380) and severity (SMD = -0.59; 95%CI -1.85, 0.66; P = 0.35, and I^2 = 88.8%; P = 0.000) of migraine but had a reduction effect on the duration of migraine attacks (WMD = -3.44; 95%CI -5.70, -1.19; P = 0.003, and I^2 = 0.0%; P = 0.926). In conclusion, omega-3 intake leads to a significant reduction of approximately 3.44 hours in the duration

of migraine. Further randomized controlled trials of high methodological quality with adequate sample sizes are required to confirm the results of the meta-analyses.

KEYWORDS: Migraine; docosahexaenoic acid; eicosapentaenoic acid; fish oil; omega-3

Arthritic Conditions

Abdulrazaq M, Innes JK, Calder PC. Effect of ω-3 polyunsaturated fatty acids on arthritic pain: A systematic review. Nutrition. 2017 Jul 1;39:57-66.

Abstract

OBJECTIVES: Pain is a significant problem in rheumatoid arthritis (RA) and is associated with prostaglandins derived from the ω-6 polyunsaturated fatty acid (PUFA) arachidonic acid. The ω-3 PUFAs eicosapentaenoic acid and docosahexaenoic acid have been shown to reduce inflammation, with some studies showing clinical improvements in RA. The aim of this systematic review was to investigate the effect of ω-3 PUFAs on arthritic pain.
METHOD: A systematic literature review of ω-3 PUFAs and pain associated with RA was performed up to December 2015. Randomized controlled trials (RCTs) investigating the effect of ω-3 PUFAs (>2 g/d) on patient or physician assessment of pain, or assessment by both patient and physician, were included. The Cochrane Collaboration's tool for assessing risk for bias was employed. Data for outcomes of interest were extracted and collated for interpretation.
RESULTS: Eighteen RCTs published between 1985 and 2013 involving 1143 patients were included. Dosage of ω-3 PUFAs used was 2.1 to 9.1 g/d, with study durations of 12 to 52 wk. Ten studies supported the hypothesis that there is a reduction in patient or physician assessment of pain associated with RA after intake of ω-3 PUFAs. Eight studies found no statistically significant effect of ω-3 PUFAs on arthritic pain.
CONCLUSIONS: ω-3 PUFAs may have a therapeutic role in decreasing pain associated with RA, with doses of 3 to 6 g/d appearing to have a greater effect. Due to the limitations identified in the RCTs included in this review, more research is needed to investigate ω-3 PUFAs in larger populations and over extended periods of time.
KEYWORDS: DHA; EPA; Fish oil; Pain; Rheumatoid arthritis

Senftleber N, Nielsen S, Andersen J, Bliddal H, Tarp S, Lauritzen L, Furst D, Suarez-Almazor M, Lyddiatt A, Christensen R. Marine oil supplements for arthritis pain: a systematic review and meta-analysis of randomized trials. Nutrients. 2017 Jan;9(1):42.

Abstract

Arthritis patients often take fish oil supplements to alleviate symptoms, but limited evidence exists regarding their efficacy. The objective was to evaluate whether marine oil supplements reduce pain and/or improve other clinical outcomes in patients with arthritis. Six databases were searched systematically (24 February 2015). We included randomized trials of oral supplements of all marine oils compared with a control in arthritis patients. The internal validity was assessed using the Cochrane Risk of Bias tool and heterogeneity was explored using restricted maximum of likelihood (REML)-based

meta-regression analysis. Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used to rate the overall quality of the evidence. Forty-two trials were included; 30 trials reported complete data on pain. The standardized mean difference (SMD) suggested a favorable effect (-0.24; 95% confidence interval, CI, -0.42 to -0.07; heterogeneity, I^2 = 63%. A significant effect was found in patients with rheumatoid arthritis (22 trials; -0.21; 95% CI, -0.42 to -0.004) and other or mixed diagnoses (3 trials; -0.63; 95% CI, -1.20 to -0.06), but not in osteoarthritis patients (5 trials; -0.17; 95% CI, -0.57-0.24). The evidence for using marine oil to alleviate pain in arthritis patients was overall of low quality, but of moderate quality in rheumatoid arthritis patients.

KEYWORDS: arthritis; complementary medicine; fish oil; joint pain; marine oil; meta-analysis; randomized controlled trials; rheumatology

Reproductive Disorders and Fertility

Yang K, Zeng L, Bao T, Ge J. Effectiveness of Omega-3 fatty acid for polycystic ovary syndrome: a systematic review and meta-analysis. Reproductive Biology and Endocrinology. 2018 Dec;16(1):27.

Abstract

OBJECTIVE: To assess the effectiveness and safety of omega-3 fatty acid for patients with PCOS.
METHODS: In this meta-analysis, data from randomized controlled trials were obtained to assess the effects of omega-3 fatty acid versus placebo or western medicine in women with PCOS. The study's registration number is CRD42017065859. The primary outcomes included the change of homeostatic model assessment (HOMA) of insulin resistance, total cholesterol (TC), triglyceride (TG) and adiponectin.
RESULT: Nine trials involving 591 patients were included. Comparing with the control group, omega-3 fatty acid may improve HOMA index (WMD -0.80; 95% CI -0.89, - 0.71; P<0. 00001), decrease TC and TG level [TC: (WMD -9.43; 95% CI -11.90, - 6.95; P<0. 00001); TG: (WMD -29.21; 95% CI -48.08, - 10.34; P = 0. 002)], and increase adiponectin level (WMD 1.34; 95% CI 0.51, 2.17; P = 0. 002).
CONCLUSION: Based on current evidence, omega-3 fatty acid may be recommended for the treatment of PCOS with insulin resistance as well as high TC (especially LDL-C) and TG.
KEYWORDS: Meta-analysis; Omega-3 fatty acid; Polycystic ovary syndrome; Systematic review

RANDOMISED CONTROLLED TRIALS

Cardiometabolic Disease and Risk

Alfaddagh A, Elajami TK, Ashfaque H, Saleh M, Bistrian BR, Welty FK. Effect of eicosapentaenoic and docosahexaenoic acids added to statin therapy on coronary artery plaque in patients with coronary artery disease: a randomized

clinical trial. J Am Heart Assoc. 2017 Dec 15;6(12). pii: e006981. doi: 10.1161/JAHA.117.006981

Abstract

BACKGROUND: Although statins reduce cardiovascular events, residual risk remains. Therefore, additional modalities are needed to reduce risk. We evaluated the effect of eicosapentaenoic acid and docosahexaenoic acid in pharmacologic doses added to statin treatment on coronary artery plaque volume.
METHODS AND RESULTS: A total of 285 subjects with stable coronary artery disease on statins were randomized to omega-3ethyl-ester (1.86 g of eicosapentaenoic acid and 1.5 g of docosahexaenoic acid daily) or no omega-3 (control) for 30 months. Coronary plaque volume was assessed by coronary computed tomographic angiography. Mean (SD) age was 63.0 (7.7) years; mean low-density lipoprotein cholesterol ≤80 mg/dL. In the intention-to-treat analysis, our primary endpoint, noncalcified plaque volume, was not different between groups (P=0.14) but approached significance in the per protocol analysis (P=0.07). When stratified by age in the intention-to-treat analysis, younger omega-3 subjects had significantly less progression of the primary endpoint, noncalcified plaque (P=0.013), and fibrous, calcified and total plaque. In plaque subtype analysis, controls had significant progression of fibrous plaque compared to no change in the omega-3 ethyl-ester group (median % change [interquartile range], 5.0% [-5.7, 20.0] versus -0.1% [-12.3, 14.5], respectively; P=0.018). Among those on low-intensity statins, omega-3 ethyl-ester subjects had attenuation of fibrous plaque progression compared to controls (median % change [interquartile range], 0.3% [-12.8, 9.0] versus 4.8% [-5.1, 19.0], respectively; P=0.032). In contrast, those on high-intensity statins had no difference in plaque change in either treatment arm.
CONCLUSIONS: High-dose eicosapentaenoic acid and docosahexaenoic acid provided additional benefit to statins in preventing progression of fibrous coronary plaque in subjects adherent to therapy with well-controlled low-density lipoprotein cholesterol levels. The benefit on low-intensity statin, but not high-intensity statin, suggests that statin intensity affects plaque volume.
CLINICAL TRIAL REGISTRATION: URL: http://www.ClinicalTrials.gov. Unique identifier: NCT01624727.

KEYWORDS: coronary computed tomography angiography; coronary plaque subtype; eicosapentaenoic acid; omega-3 fatty acids; plaque progression

Casanova MA, Medeiros F, Trindade M, Cohen C, Oigman W, Neves MF. Omega-3 fatty acids supplementation improves endothelial function and arterial stiffness in hypertensive patients with hypertriglyceridemia and high cardiovascular risk. J Am Soc Hypertens. 2017 Jan;11(1):10-19. doi: 10.1016/j.jash.2016.10.004.

Abstract

Association between hypertriglyceridemia and cardiovascular (CV) disease is still controversial. The purpose of this study was to compare omega-3 and ciprofibrate effects on the vascular structure and function in low and high CV risk hypertensive patients with

hypertriglyceridemia. Twenty-nine adults with triglycerides 150-499 mg/dL were divided into low (<7.5%) and high (≥7.5%) CV risk, randomized to receive omega-3 fatty acids 1800 mg/d or ciprofibrate 100 mg/d for 12 weeks. Treatment was switched after 8-week washout. Clinical evaluation and vascular tests were assessed at baseline and after intervention. Peripheral (131 ± 3 to 125 ± 3 mm Hg, P < .05) and aortic (124 ± 3 to 118 ± 2 mg/dL, P < .05) systolic blood pressure were decreased by ciprofibrate in low-risk patients. In high-risk patients, pulse wave velocity was reduced (10.4 ± 0.4 to 9.4 ± 0.3 m/s, P < .05) and flow-mediated dilation was increased (11.1 ± 1.6 to 13.5 ± 1.2%, P < .05) by omega-3. In conclusion, omega-3 improved arterial stiffness and endothelial function, pointing out the beneficial effect of this therapy on vascular aging, in high-risk patients.

KEYWORDS: Ciprofibrate; arterial stiffness; cardiovascular risk; hypertension; hypertriglyceridemia; omega-3 fatty acids

Kamenova, P. Improvement of insulin sensitivity in patients with type 2 diabetes mellitus after oral administration of alpha-lipoic acid. Hormones (Athens). 2006; 5, 251–258.

Kastelein JJ, Maki KC, Susekov A, Ezhov M, Nordestgaard BG, Machielse BN, et al. Omega-3 free fatty acids for the treatment of severe hypertriglyceridemia: the Epanova for Lowering Very high triglycerides (EVOLVE) trial. J Clin Lipidol. 2014 Jan-Feb;8(1):94-106. doi: 10.1016/j.jacl.2013.10.003.

Abstract

BACKGROUND: Omega-3 fatty acids in free fatty acid form have enhanced bioavailability, and plasma levels are less influenced by food than for ethyl ester forms.
OBJECTIVE: The aim was to evaluate the safety and lipid-altering efficacy in subjects with severe hypertriglyceridemia of an investigational pharmaceutical omega-3 free fatty acid (OM3-FFA) containing eicosapentaenoic acid and docosahexaenoic acid.
METHODS: This was a multinational, double-blind, randomized, out-patient study. Men and women with triglycerides (TGs) ≥ 500 mg/dL, but <2000 mg/dL, took control (olive oil [OO] 4 g/d; n = 99), OM3-FFA 2 g/d (plus OO 2 g/d; n = 100), OM3-FFA 3 g/d (plus OO 1 g/d; n = 101), or OM3-FFA 4 g/d (n = 99) capsules for 12 weeks in combination with the National Cholesterol Education Program Therapeutic Lifestyle Changes diet.
RESULTS: Fasting serum TGs changed from baseline by -25.9% (P < .01 vs OO), -25.5% (P < .01 vs OO), and -30.9% (P < .001 vs OO) with 2, 3, and 4 g/d OM3-FFA, respectively, compared with -4.3% with OO. Non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol-to-HDL-C ratio, very low-density lipoprotein cholesterol, remnant-like particle cholesterol, apolipoprotein CIII, lipoprotein-associated phospholipase A2, and arachidonic acid were significantly lowered (P < .05 at each OM3-FFA dosage vs OO); and plasma eicosapentaenoic acid and docosahexaenoic acid were significantly elevated (P < .001 at each OM3-FFA dosage vs OO). With OM3-FFA 2 and 4 g/d (but not 3 g/d), low-density lipoprotein cholesterol was significantly increased compared with OO (P < .05 vs OO). High-sensitivity C-reactive protein responses with OM3-FFA did not differ significantly from the OO response at any dosage.

Fewer subjects reported any adverse event with OO vs OM3-FFA, but frequencies across dosage groups were similar. Discontinuation due to adverse event, primarily gastrointestinal, ranged from 5% to 7% across OM3-FFA dosage groups vs 0% for OO.
CONCLUSIONS: OM3-FFA achieved the primary end point for TG lowering and secondary end point of non-HDL-C lowering at 2, 3, and 4 g/d in persons with severe hypertriglyceridemia. This trial was registered at www.clinicaltrials.gov as NCT01242527.
KEYWORDS: Hypertriglyceridemia; Low-density lipoprotein cholesterol; Omega-3 fatty acids; Remnants; Treatment; Triglycerides

Kim CH, Han KA, Yu J, Lee SH, Jeon HK, Kim SH, et al. Efficacy and safety of adding omega-3 fatty acids in statin-treated patients with residual hypertriglyceridemia: ROMANTIC (Rosuvastatin-OMAcor in residual hyperTriglyceridemia), a randomized, double-blind, and placebo-controlled trial. Clin Ther. 2018 Jan;40(1):83-94. doi: 10.1016/j.clinthera.2017.11.007.

Abstract

PURPOSE: The purpose of this study was to examine the efficacy and safety of adding ω-3 fatty acids to rosuvastatin in patients with residual hypertriglyceridemia despite statin treatment.
METHODS: This study was a multicenter, randomized, double-blind, placebo-controlled study. After a 4-week run-in period of rosuvastatin treatment, the patients who had residual hypertriglyceridemia were randomized to receive rosuvastatin 20 mg/d plus ω-3 fatty acids 4 g/d (ROSUMEGA group) or rosuvastatin 20 mg/d (rosuvastatin group) with a 1:1 ratio and were prescribed each medication for 8 weeks.
FINDINGS: A total of 201 patients were analyzed (mean [SD] age, 58.1 [10.7] years; 62.7% male). After 8 weeks of treatment, the percentage change from baseline in triglycerides (TGs) and non-HDL-C was significantly greater in the ROSUMEGA group than in the rosuvastatin group (TGs: -26.3% vs -11.4%, $P < 0.001$; non-HDL-C: -10.7% vs -2.2%, $P = 0.001$). In the linear regression analysis, the lipid-lowering effect of ω-3 fatty acids was greater when baseline TG or non-HDL-C levels were high and body mass index was low. The incidence of adverse events was not significantly different between the 2 groups.
IMPLICATIONS: In patients with residual hypertriglyceridemia despite statin treatment, a combination of ω-3 fatty acids and rosuvastatin produced a greater reduction of TGs and non-HDL-C than rosuvastatin alone. Further study is needed to determine whether the advantages of this lipid profile of ω-3 fatty acids actually leads to the prevention of cardiovascular event.
ClinicalTrials.gov identifier: NCT03026933.
KEYWORDS: combination; hypertriglyceridemia; non–HDL-C; rosuvastatin; triglycerides; ω-3 fatty acids

Marchioli R, Barzi F, Bomba E, Chieffo C, Di Gregorio D, Di Mascio R, Franzosi MG, Geraci E,Levantesi G, Maggioni AP, Mantini L, Marfisi RM, Mastrogiuseppe G, Mininni N, Nicolosi GL, Santini M, Schweiger C, Tavazzi L, Tognoni G, Tucci C, Valagussa F. GISSI-Prevenzione Investigators. Early protection against sudden death by n-3 polyunsaturated fatty acids

after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. Circulation. 2002;105:1897–1903.

McEwen BJ, Morel-Kopp MC, Tofler GH, Ward CM. The effect of omega-3 polyunsaturated fatty acids on fibrin and thrombin generation in healthy subjects and subjects with cardiovascular disease. Seminars in thrombosis and hemostasis. 2015 Apr. Vol. 41, No. 03, pp. 315-322.

Cognition

Witte AV, Kerti L, Hermannstädter HM, Fiebach JB, Schreiber SJ, Schuchardt JP, et al. Long-chain omega-3 fatty acids improve brain function and structure in older adults. Cereb Cortex. 2014 Nov;24(11):3059-68. doi: 10.1093/cercor/bht163.

Abstract

Higher intake of seafish or oil rich in long-chain omega-3 polyunsaturated fatty acids (LC-n3-FA) may be beneficial for the aging brain. We tested in a prospective interventional design whether high levels of supplementary LC-n3-FA would improve cognition, and addressed potential mechanisms underlying the effects. Sixty-five healthy subjects (50-75 years, 30 females) successfully completed 26 weeks of either fish oil (2.2 g/day LC-n3-FA) or placebo intake. Before and after the intervention period, cognitive performance, structural neuroimaging, vascular markers, and blood parameters were assayed. We found a significant increase in executive functions after LC-n3-FA compared with placebo (P = 0.023). In parallel, LC-n3-FA exerted beneficial effects on white matter microstructural integrity and gray matter volume in frontal, temporal, parietal, and limbic areas primarily of the left hemisphere, and on carotid intima media thickness and diastolic blood pressure. Improvements in executive functions correlated positively with changes in omega-3-index and peripheral brain-derived neurotrophic factor, and negatively with changes in peripheral fasting insulin. This double-blind randomized interventional study provides first-time evidence that LC-n3-FA exert positive effects on brain functions in healthy older adults, and elucidates underlying mechanisms. Our findings suggest novel strategies to maintain cognitive functions into old age.
KEYWORDS: cognitive aging; diffusion tensor imaging; executive functions; intima media thickness; voxel-based morphometry

Skin Disorders

Jung JY, Kwon HH, Hong JS, Yoon JY, Park MS, Jang MY et al. Effect of dietary supplementation with omega-3 fatty acid and gamma-linolenic acid on acne vulgaris: a randomised, double-blind, controlled trial. Acta Derm Venereol. 2014 Sep;94(5):521-5. doi: 10.2340/00015555-1802.

Abstract

This study was undertaken to evaluate the clinical efficacy, safety, and histological changes induced by dietary omega-3 fatty acid and γ-linoleic acid in acne vulgaris. A 10-week, randomised, controlled parallel dietary intervention study was performed in 45 participants with mild to moderate acne, which were allocated to either an omega-3 fatty acid group (2,000 mg of eicosapentaenoic acid and docosahexaenoic acid), a γ-linoleic acid group (borage oil containing 400 mg γ-linoleic acid), or a control group. After 10 weeks of omega-3 fatty acid or γ-linoleic acid supplementation, inflammatory and non-inflammatory acne lesions decreased significantly. Patient subjective assessment of improvement showed a similar result. Heamatoxylin & eosin staining of acne lesions demonstrated reductions in inflammation and immunohistochemical staining intensity for interleukin-8. No severe adverse effect was reported. This study shows for the first time that omega-3 fatty acid and γ-linoleic acid could be used as adjuvant treatments for acne patients.

Pregnancy

Bisgaard H, Stokholm J, Chawes BL, Vissing NH, Bjarnadóttir E, Schoos AM, et al. Fish oil-derived fatty acids in pregnancy and wheeze and asthma in offspring. N Engl J Med. 2016 Dec 29;375(26):2530-9. doi: 10.1056/NEJMoa1503734.

Abstract

BACKGROUND: Reduced intake of n-3 long-chain polyunsaturated fatty acids (LCPUFAs) may be a contributing factor to the increasing prevalence of wheezing disorders. We assessed the effect of supplementation with n-3 LCPUFAs in pregnant women on the risk of persistent wheeze and asthma in their offspring.
METHODS: We randomly assigned 736 pregnant women at 24 weeks of gestation to receive 2.4 g of n-3 LCPUFA (fish oil) or placebo (olive oil) per day. Their children formed the Copenhagen Prospective Studies on Asthma in Childhood2010 (COPSAC2010) cohort and were followed prospectively with extensive clinical phenotyping. Neither the investigators nor the participants were aware of group assignments during follow-up for the first 3 years of the children's lives, after which there was a 2-year follow-up period during which only the investigators were unaware of group assignments. The primary end point was persistent wheeze or asthma, and the secondary end points included lower respiratory tract infections, asthma exacerbations, eczema, and allergic sensitization.
RESULTS: A total of 695 children were included in the trial, and 95.5% completed the 3-year, double-blind follow-up period. The risk of persistent wheeze or asthma in the treatment group was 16.9%, versus 23.7% in the control group (hazard ratio, 0.69; 95% confidence interval [CI], 0.49 to 0.97; P=0.035), corresponding to a relative reduction of 30.7%. Prespecified subgroup analyses suggested that the effect was strongest in the children of women whose blood levels of eicosapentaenoic acid and docosahexaenoic acid were in the lowest third of the trial population at randomization: 17.5% versus 34.1% (hazard ratio, 0.46; 95% CI, 0.25 to 0.83; P=0.011). Analyses of secondary end points showed that supplementation with n-3 LCPUFA was associated with a reduced risk of infections of the lower respiratory tract (31.7% vs. 39.1%; hazard ratio, 0.75; 95% CI, 0.58

to 0.98; P=0.033), but there was no statistically significant association between supplementation and asthma exacerbations, eczema, or allergic sensitization.
CONCLUSIONS: Supplementation with n-3 LCPUFA in the third trimester of pregnancy reduced the absolute risk of persistent wheeze or asthma and infections of the lower respiratory tract in offspring by approximately 7 percentage points, or one third. (ClinicalTrials.gov number, NCT00798226.).

Haghiac M, Yang XH, Presley L, Smith S, Dettelback S, Minium J, et al. Dietary omega-3 fatty acid supplementation reduces inflammation in obese pregnant women: a randomized double-blind controlled clinical trial. PLoS One. 2015 Sep 4;10(9):e0137309. doi: 10.1371/journal.pone.0137309.

Abstract

OBJECTIVE: Long-chain omega 3 fatty acids, eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3) exert potent anti-inflammatory properties in humans. This study characterized the effects of omega-3 ω-3 fatty acids supplements (ω-3 FA) on the inflammatory status in the placenta and adipose tissue of overweight/obese pregnant women.
STUDY DESIGN: A randomized, double-masked controlled trial was conducted in overweight/obese pregnant women that were randomly assigned to receive DHA plus EPA (2 g/day) or the equivalent of a placebo twice a day from week 10-16 to term. Inflammatory pathways were characterized in: 1) adipose tissue and placenta of treated vs. untreated women; and 2) adipose and trophoblast cells cultured with long chain FAs.
RESULTS: The sum of plasma DHA and EPA increased by 5.8 fold and ω-3 FA/ω-6 FA ratio was 1.5 in treated vs. untreated women ($p< 0.005$). Plasma CRP concentrations were reduced ($p<0.001$). The adipose tissue and placenta of treated women exhibited a significant decrease in TLR4 adipose and placental expression as well as IL6, IL8, and TNFα In vitro, EPA and DHA suppressed the activation of TLR4, IL6, IL8 induced by palmitate in culture of adipose and trophoblast cells.
CONCLUSION: Supplementation of overweight/obese pregnant women with dietary ω-3 FAs for >25 weeks reduced inflammation in maternal adipose and the placental tissue. TLR4 appears as a central target of the anti-inflammatory effects at the cellular level.
TRIAL REGISTRATION: ClinicalTrials.gov NCT00957476.

Hansen S, Strøm M, Maslova E, Dahl R, Hoffmann HJ, Rytter D, et al. Fish oil supplementation during pregnancy and allergic respiratory disease in the adult offspring. J Allergy Clin Immunol. 2017 Jan;139(1):104-111.e4. doi: 10.1016/j.jaci.2016.02.042.

Abstract

BACKGROUND: Maternal supplementation with long-chain n-3 polyunsaturated fatty acids can have immunologic effects on the developing fetus through several anti-inflammatory pathways. However, there is limited knowledge of the long-term programming effects.

OBJECTIVE: In a randomized controlled trial from 1990 with 24 years of follow-up, our aim was to determine whether supplementation with 2.7 g of long-chain n-3 polyunsaturated fatty acids in pregnancy can reduce the risk of asthma in offspring and allergic respiratory disease.
METHODS: The randomized controlled trial included 533 women who were randomly assigned to receive fish oil during the third trimester of pregnancy, olive oil, or no oil in the ratio 2:1:1. The offspring were followed in a mandatory national prescription register, with complete follow-up for prescriptions related to the treatment of asthma and allergic rhinitis as primary outcomes. Furthermore, the offspring were invited to complete a questionnaire (74% participated) and attend a clinical examination (47% participated) at age 18 to 19 years.
RESULTS: In intention-to-treat analyses the probability of having had asthma medication prescribed was significantly reduced in the fish oil group compared with the olive oil group (hazard ratio, 0.54, 95% CI, 0.32-0.90; P = .02). The probability of having had allergic rhinitis medication prescribed was also reduced in the fish oil group compared with the olive oil group (hazard ratio, 0.70, 95% CI, 0.47-1.05; P = .09), but the difference was not statistically significant. Self-reported information collected at age 18 to 19 years supported these findings. No associations were detected with respect to lung function outcomes or allergic sensitization at 18 to 19 years of age.
CONCLUSION: Maternal supplementation with fish oil might have prophylactic potential for long-term prevention of asthma in offspring.
KEYWORDS: Randomized controlled trial; allergies; asthma; fetal programming; long-chain n-3 polyunsaturated fatty acids

Jamilian M, Samimi M, Ebrahimi FA, Hashemi T, Taghizadeh M, Razavi M, et al. The effects of vitamin D and omega-3 fatty acid co-supplementation on glycemic control and lipid concentrations in patients with gestational diabetes. J Clin Lipidol. 2017 Mar - Apr;11(2):459-468. doi: 10.1016/j.jacl.2017.01.011.

Abstract

OBJECTIVE: This study was performed to evaluate the effects of vitamin D and omega-3 fatty acids co-supplementation on glucose metabolism and lipid concentrations in gestational diabetes (GDM) patients.
METHODS: This randomized double-blind placebo-controlled clinical trial was done among 140 GDM patients. Participants were randomly divided into 4 groups to receive: (1) 1000 mg omega-3 fatty acids containing 360 mg eicosapentaenoic acid and 240 mg docosahexaenoic acid (DHA) twice a day + vitamin D placebo (n = 35); (2) 50,000 IU vitamin D every 2 weeks + omega-3 fatty acids placebo (n = 35); (3) 50,000 IU vitamin D every 2 weeks + 1000 mg omega-3 fatty acids twice a day (n = 35), and (4) vitamin D placebo + omega-3 fatty acids placebo (n = 35) for 6 weeks.
RESULTS: After 6 weeks of intervention, patients who received combined vitamin D and omega-3 fatty acids supplements compared with vitamin D, omega-3 fatty acids, and placebo had significantly decreased fasting plasma glucose (-7.3 ± 7.8, -6.9 ± 6.6, -4.0 ± 2.5, and +1.0 ± 11.4 mg/dL, respectively, P < .001), serum insulin levels (-1.9 ± 1.9, -1.3 ±

6.3, -0.4 ± 6.3, and +2.6 ± 6.5 μIU/mL, respectively, P = .005), homeostatic model of assessment for insulin resistance (-0.7 ± 0.6, -0.5 ± 1.4, -0.2 ± 1.5, and +0.6 ± 1.5, respectively, P < .001) and increased quantitative insulin sensitivity check index (+0.01 ± 0.01, +0.008 ± 0.02, +0.002 ± 0.02, and -0.005 ± 0.02, respectively, P = .001). In addition, changes in serum triglycerides (-8.2 ± 41.0, +7.6 ± 31.5, +3.6 ± 29.9, and +20.1 ± 29.6 mg/dL, respectively, P = .006) and very low-density lipoprotein cholesterol (-1.6 ± 8.2, +1.5 ± 6.3, +0.8 ± 6.0, and +4.0 ± 5.9 mg/dL, respectively, P = .006) in the vitamin D plus omega-3 fatty acids group were significantly different from the changes in these indicators in the vitamin D, omega-3 fatty acids, and placebo groups.
CONCLUSION: Overall, vitamin D and omega-3 fatty acids co-supplementation for 6 weeks among GDM patients had beneficial effects on fasting plasma glucose, serum insulin levels, homeostatic model of assessment for insulin resistance, quantitative insulin sensitivity check index, serum triglycerides, and very low-density lipoprotein cholesterol levels.
KEYWORDS: Gestational diabetes; Glycemic control; Lipid concentrations; Omega-3 fatty acid; Supplementation; Vitamin D

Respiratory

MacRedmond R, Singhera G, Attridge S, Bahzad M, Fava C, Lai Y, Hallstrand TS, Dorscheid DR. Conjugated linoleic acid improves airway hyper-reactivity in overweight mild asthmatics. Clinical & Experimental Allergy. 2010; 40: 1071–1078. doi:10.1111/j.1365-2222.2010.03531.x

Mickleborough TD, Lindley MR, Ionescu AA, Fly AD. Protective effect of fish oil supplementation on exercise-induced bronchoconstriction in asthma. Chest. 2006; 129, 39–49. PubMed doi:10.1378/chest.129.1.39.

Arthritic Disorders

Kristensen S, Schmidt EB, Schlemmer A, Rasmussen C, Johansen MB, Christensen JH. Beneficial effect of n-3 polyunsaturated fatty acids on inflammation and analgesic use in psoriatic arthritis: a randomized, double blind, placebo-controlled trial. Scand J Rheumatol. 2018 Jan;47(1):27-36. doi: 10.1080/03009742.2017.1287304.

Abstract

OBJECTIVE: This study aimed to investigate the effects of marine n-3 polyunsaturated fatty acids (PUFAs) on disease activity, use of analgesics, and inflammatory biomarkers in patients with psoriatic arthritis (PsA).
METHOD: Patients with established PsA (n = 145) were investigated in a randomized, double-blind, placebo-controlled study. The participants received a supplement of 3 g n-3 PUFA/day or 3 g olive oil/day (control) for 24 weeks. Outcome measures for disease activity, use of analgesics, and leukotriene formation from activated granulocytes were assessed at baseline and at study end.
RESULTS: In total, 145 patients were included and 133 completed the study. After 24

weeks, the n-3 PUFA group showed a decrease in Disease Activity Score (DAS28-CRP), 68 tender joint count, enthesitis score, and psoriasis area and severity index, although not significantly different from the controls. There was a significant reduction in non-steroidal anti-inflammatory drug (NSAID) and paracetamol use compared with controls ($p = 0.04$). In addition, the participants in the n-3 PUFA group had significantly lower formation of leukotriene B4 ($p = 0.004$) from stimulated granulocytes and significantly higher formation of leukotriene B5 ($p < 0.001$) compared with controls.
CONCLUSION: The n-3 PUFA-supplemented group showed improvement in outcome measures for disease activity, although the difference between the groups was not statistically significant. However, use of NSAIDs and paracetamol was significantly reduced in the n-3 PUFA group compared to the control group. Finally, there was a significant decrease in leukotriene B4 formation in the n-3 PUFA group compared with controls.

Maroon J.C., Boost J. W., Omega 3 (fish oil) fatty acids as an anti-inflammatory: an alternative to non-steroidal anti-inflammatory drugs for discogenic pain, Surgical Neurology 65. 2006; 326–331.

Rajaei E, Mowla K, Ghorbani A, Bahadoram S, Bahadoram M, Dargahi-Malamir M. The effect of omega-3 fatty acids in patients with active rheumatoid arthritis receiving DMARDS therapy: double-blind randomized controlled trial. Glob J Health Sci. 2015 Nov 3;8(7):18-25. doi: 10.5539/gjhs.v8n7p18.

Abstract

BACKGROUND: Rheumatoid arthritis is a symmetric peripheral polyarthritis of unknown etiology that, untreated or if unresponsive the therapy, typically leads to deformity and destruction of joints due to erosion of cartilage and bone. Omega-3 fatty acids have been shown to reduce morning stiffness, the number of tender joints and swollen joints in patients with rheumatoid arthritis. This study is designed for evaluation of omega-3 effects on disease activity and remission of rheumatoid arthritis in DMARDs treated patients and on weight changes and reduction of analgesic drugs consumption versus placebo.
METHODS: Sixty patients with active rheumatoid arthritis (49 female and 11 male) underwent rheumatologist examination and disease activity score were calculated. Then patients were enrolled in this 12 week, double blind, randomized, placebo- controlled study. The patients in both groups continued their pre study standard treatment. The patients were visited every 4 weeks, 4 times and data were recorded.
RESULTS: Significant improvement in the patient's global evaluation and in the physician's assessment of disease was observed in those taking omega-3. The proportions of patients who improved and of those who were able to reduce their concomitant analgesic medication were significantly greater with omega-3 consumption. There were no weight changes.
CONCLUSION: Daily supplementation with omega-3 results has significant clinical benefit and may reduce the need for concomitant analgesic consumption without weight changes.

Veselinovic M, Vasiljevic D, Vucic V, Arsic A, Petrovic S, Tomic-Lucic A, Savic M, Zivanovic S, Stojic V, Jakovljevic V. Clinical benefits of n-3 PUFA

and ϒ-linolenic acid in patients with rheumatoid arthritis. Nutrients. 2017;9(4):325.

Abstract

Background: Marine *n*-3 polyunsaturated fatty acids (PUFA) and ϒ-linolenic acid (GLA) are well-known anti-inflammatory agents that may help in the treatment of inflammatory disorders. Their effects were examined in patients with rheumatoid arthritis; (2) Methods: Sixty patients with active rheumatoid arthritis were involved in a prospective, randomized trial of a 12 week supplementation with fish oil (group I), fish oil with primrose evening oil (group II), or with no supplementation (group III). Clinical and laboratory evaluations were done at the beginning and at the end of the study; (3) Results: The Disease Activity Score 28 (DAS 28 score), number of tender joints and visual analogue scale (VAS) score decreased notably after supplementation in groups I and II ($p < 0.001$). In plasma phospholipids the *n*-6/*n*-3 fatty acids ratio declined from 15.47 ± 5.51 to 10.62 ± 5.07 ($p = 0.005$), and from 18.15 ± 5.04 to 13.50 ± 4.81 ($p = 0.005$) in groups I and II respectively. The combination of *n*-3 PUFA and GLA (group II) increased ϒ-linolenic acid (0.00 ± 0.00 to 0.13 ± 0.11, $p < 0.001$), which was undetectable in all groups before the treatments; (4) Conclusion: Daily supplementation with *n*-3 fatty acids alone or in combination with GLA exerted significant clinical benefits and certain changes in disease activity.

Vishal AA, Mishra A, Raychaudhuri SP. A double blind, randomized, placebo controlled clinical study evaluates the early efficacy of aflapin in subjects with osteoarthritis of knee. Int J Med Sci. 2011; 8:615–22.

Fertility and Reproductive Disorders

Mirmasoumi G, Fazilati M, Foroozanfard F, Vahedpoor Z, Mahmoodi S, Taghizadeh M, et al. The effects of flaxseed oil omega-3 fatty acids supplementation on metabolic status of patients with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. Exp Clin Endocrinol Diabetes. 2018 Apr;126(4):222-228. doi: 10.1055/s-0043-119751.

Abstract

OBJECTIVE: This study was conducted to evaluate the effects of flaxseed oil omega-3 fatty acids supplementation on metabolic status of patients with polycystic ovary syndrome (PCOS).
METHODS: This randomized double-blind, placebo-controlled trial was conducted on 60 women with PCOS according to the Rotterdam criteria aged 18-40 years old. Participants were randomly assigned into two groups to receive either 1,000 mg flaxseed oil omega-3 fatty acids (n=30) or placebo (n=30) twice a day for 12 weeks. Metabolic, endocrine, inflammatory factors were quantified at baseline and after the 12-week intervention.
RESULTS: After the 12-week intervention, compared to the placebo, flaxseed oil omega-3

supplementation significantly decreased insulin values (-2.6±7.7 vs.+1.3±3.9 μIU/mL, P=0.01), homeostasis model of assessment-estimated insulin resistance (-0.7±1.7 vs.+0.3±0.9, P=0.01), mF-G scores (-1.2±1.7 vs. -0.1±0.4, P=0.001), and increased quantitative insulin sensitivity check index (+0.01±0.02 vs. -0.01±0.02, P=0.01). In addition, supplementation with flaxseed oil omega-3 resulted in significant decreases in serum triglycerides (-5.1±20.9 vs.+9.7±26.1 mg/dL, P=0.01), VLDL-cholesterol (-1.0±4.2 vs.+1.9±5.2 mg/dL, P=0.01) and high-sensitivity C-reactive protein (hs-CRP) (-1.6±3.1 vs.+0.2±1.5 mg/L, P=0.004) compared to the placebo. We did not see any significant effect of flaxseed oil omega-3 supplementation on hormonal and other lipid profiles, and plasma nitric oxide levels.
CONCLUSIONS: Overall, flaxseed oil omega-3 supplementation for 12 weeks in women with PCOS had beneficial effects on insulin metabolism, mF-G scores, serum triglycerides, VLDL-cholesterol and hs-CRP levels, but did not affect hormonal and other lipid profiles, and plasma nitric oxide levels.

Moran LJ, Tsagareli V, Noakes M, Norman R. Altered preconception fatty acid intake is associated with improved pregnancy rates in overweight and obese women undertaking in vitro fertilisation. Nutrients. 2016 Jan 4;8(1). pii: E10. doi: 10.3390/nu8010010.

Abstract

Maternal preconception diet is proposed to affect fertility. Prior research assessing the effect of altering the fatty acid profile on female fertility is conflicting. The aim of this study was to assess the effect of preconception maternal diet, specifically fatty acid profile, on pregnancies and live births following in vitro fertilisation (IVF). Forty-six overweight and obese women undergoing IVF were randomised to a diet and physical activity intervention (intervention) or standard care (control). Outcome measures included pregnancy, live birth and pre-study dietary intake from food frequency questionnaire. Twenty pregnancies (n = 12/18 vs. n = 8/20, p = 0.12) and 12 live births (n = 7/18 vs. n = 5/20, p = 0.48) occurred following the intervention with no differences between the treatment groups. On analysis adjusted for BMI and smoking status, women who became pregnant had higher levels of polyunsaturated fatty acid (PUFA) intake (p = 0.03), specifically omega-6 PUFA and linoleic acid (LA) (p = 0.045) with a trend for an elevated intake of omega-3 PUFA (p = 0.06). There were no dietary differences for women who did or did not have a live birth. Maternal preconception PUFA, and specifically omega-6 and LA intake, are associated with improved pregnancy rates in overweight and obese women undergoing IVF. This has implications for optimising fertility through preconception nutrition.
KEYWORDS: assisted reproductive technology; diet; exercise; fertility; in-vitro fertilization; omega 3 fatty acids; pregnancy; unsaturated fat; weight loss

AMINO ACIDS

OVERVIEWS

Neuropsychiatric Disorders and Addiction

Asevedo E, Mendes AC, Berk M, Brietzke E. Systematic review of N-acetylcysteine in the treatment of addictions. Braz J Psychiatry. 2014 Apr-Jun;36(2):168-75.

Abstract

OBJECTIVE: To conduct the first systematic literature review of clinical trials of N-acetylcysteine (NAC) for the treatment of substance abuse disorders and addictive behaviors.
METHODS: A search of the MEDLINE, Embase and PsycINFO databases was conducted. The inclusion criteria for the review were clinical trials that used NAC in the treatment of a disorder related to substance use and/or addictive behaviors, limited to texts in English, Spanish, or French. The selected studies were evaluated with respect to type of trial, sample size, diagnostic input, intervention, length of follow-up, outcome variables, and results.
RESULTS: Nine studies analyzing a total of 165 patients met the eligibility criteria and were included in qualitative analysis. These studies evaluated the role of NAC in cocaine dependence (three studies), cannabis dependence (two studies), nicotine dependence (two studies), methamphetamine addiction (one study), and pathological gambling (one study). Five of these trials were double-blind, randomized, and placebo-controlled.
CONCLUSIONS: The studies analyzed suggest a potential role for NAC in the treatment of addiction, especially of cocaine and cannabis dependence. These results are concordant with the hypothesis of the involvement of glutamatergic pathways in the pathophysiology of addiction.

Couto JP, Moreira R. Oral N-acetylcysteine in the treatment of obsessive-compulsive disorder: a systematic review of the clinical evidence. Prog Neuropsychopharmacol Biol Psychiatry. 2018 Aug 30;86:245-254. doi: 10.1016/j.pnpbp.2018.06.005.

Abstract

Obsessive-compulsive disorder (OCD) is characterized by the presence of obsessions and/or compulsions. It is a leading cause of morbidity worldwide, as it can interfere with all aspects of life. Despite the adequate treatment trials, half of patients preserve residual or impairing symptoms and selective serotonin reuptake inhibitors (SSRIs) are not free from adverse side effects. This work aims to systematically review the current evidence available concerning the efficacy of N-acetylcysteine (NAC) in the treatment of OCD. Five randomized placebo-controlled trials (RCTs), 3 case reports and 2 case series were included. The studies developed so far are somehow contradictory. However, our pooled result from the 4 observational studies (n = 13) showed a mean reduction in Y-BOCS score after NAC treatment of -11 points (p = .01). Pooled mean difference from 4 of the 5 RCTs included was 3.35, with a95% confidence interval of -0.21-6.91 and a p-value barely below statistical significance (p = .07). This result trends to favour the use of NAC over placebo in OCD patients. NAC has an optimal tolerability profile, even in higher doses, and the most frequently reported adverse events were gastrointestinal. Despite the degree of evidence being D, in our opinion the potential of NAC is underestimated.

Considering its exceptional tolerability profile, the use as an add-on agent should be contemplated, on an ad hoc basis.

KEYWORDS: N-acetylcysteine; Nutraceutical; Obsessive-compulsive disorder

Duailibi MS, Cordeiro Q, Brietzke E, Ribeiro M, LaRowe S, Berk M, Trevizol AP. N-acetylcysteine in the treatment of craving in substance use disorders: Systematic review and meta-analysis. The American journal on addictions. 2017 Oct;26(7):660-6.

Abstract

BACKGROUND AND OBJECTIVES: Recent neurobiological evidences along with clinical observations justify the use of N-acetylcysteine (NAC) as a medication for craving. The objective of our study was to assess the evidence of efficacy of NAC for craving in substance use disorders in randomized clinical trials (RCTs).
METHODS: Systematic review of the RCTs literature (PROSPERO number 56698) until February, 2017, using MEDLINE, Cochrane Library and clinicaltrials.gov. We included seven RCTs (n = 245); most with small-to-moderate sample sizes. The main outcome was the Hedges' g for continuous scores in a random-effects model. Heterogeneity was evaluated with the I2 and the χ2 test. Publication bias was evaluated using the Begg's funnel plot and the Egger's test. Meta-regression was performed using the random-effects model.
RESULTS: Comparing NAC versus placebo, NAC was significantly superior for craving symptoms (Hedges' g = 0.94; 95%CI 0.55-1.33). The funnel plot showed the risk of publication bias was low and between-study heterogeneity was not significant (I2 = 44.4%, p = 0.07 for the χ2test). A subgroup analysis performed using meta-regression showed no particular influence.
DISCUSSION AND CONCLUSIONS: NAC was superior to placebo for craving reduction in SUDs. The relatively small number of trials and their heterogeneous methodology were possible limitations; however, these positive thrilling results stimulate further studies for clarifying the potential impact of NAC for craving symptoms in SUDs.
SCIENTIFIC SIGNIFICANCE: The safety profile of NAC and its favorable tolerability, in addition to being an over-the-counter medication, presents with an interesting potential clinical use for craving in SUDs. (Am J Addict 2017;26:660-666).

Fernandes BS, Dean OM, Dodd S, Malhi GS, Berk M. N-Acetylcysteine in depressive symptoms and functionality: a systematic review and meta-analysis. J Clin Psychiatry. 2016 Apr;77(4):e457-66. doi: 10.4088/JCP.15r09984.

Abstract

OBJECTIVE: To assess the utility of N-acetylcysteine administration for depressive symptoms in subjects with psychiatric conditions using a systematic review and meta-

analysis.
DATA SOURCES: A computerized literature search was conducted in MEDLINE, Embase, the Cochrane Library, SciELO, PsycINFO, Scopus, and Web of Knowledge. No year or country restrictions were used. The Boolean terms used for the electronic database search were (NACOR N-acetylcysteine OR acetylcysteine) AND (depression OR depressive OR depressed) AND (trial). The last search was performed in November 2014.
STUDY SELECTION: The literature was searched for double-blind, randomized, placebo-controlled trials using N-acetylcysteine for depressive symptoms regardless of the main psychiatric condition. Using keywords and cross-referenced bibliographies, 38 studies were identified and examined in depth. Of those, 33 articles were rejected because inclusion criteria were not met. Finally, 5 studies were included.
DATA EXTRACTION: Data were extracted independently by 2 investigators. The primary outcome measure was change in depressive symptoms. Functionality, quality of life, and manic and anxiety symptoms were also examined. A full review and meta-analysis were performed. Standardized mean differences (SMDs) and odds ratios (ORs) with 95% CIs were calculated.
RESULTS: Five studies fulfilled our inclusion criteria for the meta-analysis, providing data on 574 participants, of whom 291 were randomized to receive N-acetylcysteine and 283 to placebo. The follow-up varied from 12 to 24 weeks. Two studies included subjects with bipolar disorder and current depressive symptoms, 1 included subjects with MDD in a current depressive episode, and 2 included subjects with depressive symptoms in the context of other psychiatric conditions (1 trichotillomania and 1 heavy smoking). Treatment with N-acetylcysteine improved depressive symptoms as assessed by Montgomery-Asberg Depression Rating Scale and Hamilton Depression Rating Scale when compared to placebo (SMD = 0.37; 95% CI = 0.19 to 0.55; P < .001). Subjects receiving N-acetylcysteine had better depressive symptoms scores on the Clinical Global Impressions-Severity of Illness scale at follow-up than subjects on placebo (SMD = 0.22; 95% CI = 0.03 to 0.41; P < .001). In addition, global functionality was better in N-acetylcysteine than in placebo conditions. There were no changes in quality of life. With regard to adverse events, only minor adverse events were associated with N-acetylcysteine (OR = 1.61; 95% CI = 1.01 to 2.59; P = .049).
CONCLUSIONS: Administration of N-acetylcysteine ameliorates depressive symptoms, improves functionality, and shows good tolerability.

Nocito Echevarria MA, Andrade Reis T, Ruffo Capatti G, Siciliano Soares V, da Silveira DX, Fidalgo TM. N-acetylcysteine for treating cocaine addiction - A systematic review. Psychiatry Res. 2017 May;251:197-203. doi: 10.1016/j.psychres.2017.02.024.

Abstract

The aim of this paper is to extensively review the current literature available on N-acetylcysteine (NAC) treatment for cocaine dependence (clinical and experimental studies). We screened all articles published before February 2016 reporting on the use of NAC as a pharmacological intervention for cocaine dependence or discussed its potential as a

therapeutic approach for cocaine dependence. We described our results qualitatively. 21 studies matched our search criteria: 6 clinical trials and 15 animal studies. Four clinical studies showed NAC's capacity to reduce craving, desire to use cocaine, cocaine-cue viewing-time and cocaine-related spending. Studies in animal models also support this reinstatement prevention application of NAC. NAC reverses the disruption of glutamate homeostasis caused by long-term cocaine use restoring function of the cystine-glutamate exchanger in glial cells and reversing the downregulated GLT-1 receptor. Current data suggest promising potential for NAC as an anti-relapse agent, as a double-blind placebo trial was mainly negative, except in the subgroup of patients who were already abstinent. An optimal dose for relapse prevention may be one that restores extrasynaptic glutamate to physiological levels and predominantly activates mGluR2 and 3, but not mGluR5 receptors, which are linked to relapse. NAC may be better suited for avoiding relapse in already abstinent subjects.

Oliver G, Dean O, Camfield D, Blair-West S, Ng C, Berk M, Sarris J. N-acetyl cysteine in the treatment of obsessive compulsive and related disorders: a systematic review. Clinical Psychopharmacology and Neuroscience. 2015 Apr;13(1):12.

Abstract

OBJECTIVE: Obsessive compulsive and related disorders are a collection of debilitating psychiatric disorders in which the role of glutamate dysfunction in the underpinning neurobiology is becoming well established. N-acetyl cysteine (NAC) is a glutamate modulator with promising therapeutic effect. This paper presents a systematic review of clinical trials and case reports exploring the use of NAC for these disorders. A further objective was to detail the methodology of current clinical trials being conducted in the area.
METHODS: PubMed, Web of Science and Cochrane Library Database were searched for human clinical trials or case reports investigating NAC in the treatment of obsessive compulsive disorder (OCD) or obsessive compulsive related disorders. Researchers with known involvement in NAC studies were contacted for any unpublished data.
RESULTS: Four clinical trials and five case reports/series were identified. Study durations were commonly 12-weeks, using 2,400-3,000 mg/day of NAC. Overall, NAC demonstrates activity in reducing the severity of symptoms, with a good tolerability profile and minimal adverse effects. Currently there are three ongoing randomized controlled trials using NAC for OCD (two adults and one pediatric), and one for excoriation.
CONCLUSIONS: Encouraging results have been demonstrated from the few pilot studies that have been conducted. These results are detailed, in addition to a discussion of future potential research.

KEYWORDS: Glutamate; Obsessive-compulsive disorder; Review; Trichotillomania; acetylcysteine; systematic

Zheng W, Zhang QE, Cai DB, Yang XH, Qiu Y, Ungvari GS. N-acetylcysteine for major mental disorders: a systematic review and meta-analysis of randomized

controlled trials. Acta Psychiatr Scand. 2018 May;137(5):391-400. doi: 10.1111/acps.12862.

Abstract

OBJECTIVE: This systematic review and meta-analysis of randomized controlled trials (RCTs) examined the efficacy and safety of adjunctive N-acetylcysteine (NAC), an antioxidant drug, in treating major depressive disorder (MDD), bipolar disorder, and schizophrenia.
METHODS: The PubMed, Cochrane Library, PsycINFO, CNKI, CBM, and WanFang databases were independently searched and screened by two researchers. Standardized mean differences (SMDs), risk ratios, and their 95% confidence intervals (CIs) were computed.
RESULTS: Six RCTs (n = 701) of NAC for schizophrenia (three RCTs, n = 307), bipolar disorder (two RCTs, n = 125), and MDD (one RCT, n = 269) were identified and analyzed as separate groups. Adjunctive NAC significantly improved total psychopathology (SMD = -0.74, 95% CI: -1.43, -0.06; I2 = 84%, P = 0.03) in schizophrenia, but it had no significant effect on depressive and manic symptoms as assessed by the Young Mania Rating Scale in bipolar disorder and only a small effect on major depressive symptoms. Adverse drug reactions to NAC and discontinuation rates between the NAC and control groups were similar across the three disorders.
CONCLUSIONS: Adjunctive NAC appears to be a safe treatment that has efficacy for schizophrenia, but not for bipolar disorder or MDD. Further higher quality RCTs are warranted to determine the role of adjunctive NAC in the treatment of major psychiatric disorders.
KEYWORDS: N-acetylcysteine; bipolar disorder; major depressive disorder; oxidative stress; schizophrenia

Chronic Pancreatitis

Talukdar R, Murthy HV, Reddy DN. Role of methionine containing antioxidant combination in the management of pain in chronic pancreatitis: a systematic review and meta-analysis. Pancreatology. 2015 Mar 1;15(2):136-44.

Abstract

BACKGROUND: Pain in CP results from inflammation and neuroimmune alterations that are associated with oxidative stress, among other mechanisms. This is marked by depletion of antioxidant defenses including methionine, which is a donor of methyl moieties that maintains the acinar transsulfuration pathway. We performed a systematic review and meta-analysis of trials evaluating methionine-containing antioxidants in CP.
PATIENT AND METHODS: Literature search was conducted in Medline/Pubmed, EMBASE, and Cochrane databases. Systematic review and meta-analysis was performed per PRISMA guidelines. Main study outcome was pain relief. GRADE system was used for quality assessment. Heterogeneity was assessed by the Q and I(2) measures; publication bias by Egger's test. Random-effect model (DerSimonian and Laird) was used if there was heterogeneity.

RESULTS: Eight studies (n = 411) were identified that used methionine-containing antioxidants. The study duration ranged from 10 wks to 12 months. All studies used methionine, organic selenium, ascorbate, beta-carotene and alpha-tocoferol. Four studies (including two RCTs) that reported change in pain scores were metaanalyzed. Though overall effect [standardized difference in means (95% CI)] on pain score reduction was -0.95 (-1.738 to -0.160) (z = -2.36; p = 0.018), the significance was lost when the two RCTs were meta-analyzed. RCTs that reported the number of pain free patients had a statistically significant overall effect of -3.204 (p = 0.001). Though more patients on methionine containing antioxidants had adverse events, majority of them were mild. **CONCLUSION:** Methionine containing antioxidants appear to result in pain reduction in a significant proportion of CP patients. Further randomized controlled trials with homogeneous outcome measures are needed.

KEYWORDS: Antioxidant combination; Chronic pancreatitis; Meta-analysis; Methionine; Pain; Systematic review

Respiratory Disorders

Cazzola M, Calzetta L, Page C, Jardim J, Chuchalin AG, Rogliani P et al. Influence of N-acetylcysteine on chronic bronchitis or COPD exacerbations: a meta-analysis. Eur Respir Rev. 2015 Sep;24(137):451-61. doi: 10.1183/16000617.00002215.

Abstract

In order to clarify the possible role of N-acetylcysteine (NAC) in the treatment of patients with chronic bronchitis and chronic obstructive pulmonary disease (COPD), we have carried out a meta-analysis testing the available evidence that NAC treatment may be effective in preventing exacerbations of chronic bronchitis or COPD and evaluating whether there is a substantial difference between the responses induced by low (≤ 600 mg per day) and high (> 600 mg per day) doses of NAC. The results of the present meta-analysis (13 studies, 4155 COPD patients, NAC n = 1933; placebo or controls n = 2222) showed that patients treated with NAC had significantly and consistently fewer exacerbations of chronic bronchitis or COPD (relative risk 0.75, 95% CI 0.66-0.84; p < 0.01), although this protective effect was more apparent in patients without evidence of airway obstruction. However, high doses of NAC were also effective in patients suffering from COPD diagnosed using spirometric criteria (relative risk 0.75, 95% CI 0.68-0.82; p = 0.04). NAC was well tolerated and the risk of adverse reactions was not dose-dependent (low doses relative risk 0.93, 95% CI 0.89-0.97; p = 0.40; high doses relative risk 1.11, 95% CI 0.89-1.39; p = 0.58). The strong signal that comes from this meta-analysis leads us to state that if a patient suffering from chronic bronchitis presents a documented airway obstruction, NAC should be administered at a dose of ≥ 1200 mg per day to prevent exacerbations, while if a patient suffers from chronic bronchitis, but is without airway obstruction, a regular treatment of 600 mg per day seems to be sufficient.

Fen F, Zhang J, Wang Z, Wu Q, Zhou X. Efficacy and safety of N-acetylcysteine therapy for idiopathic pulmonary fibrosis: An updated

systematic review and meta-analysis. Experimental and Therapeutic Medicine. 2019 Jul 1;18(1):802-16.

Abstract

Idiopathic pulmonary fibrosis (IPF) is a progressive and ultimately fatal lung disease with poor prognosis and limited treatment options. *N*-acetylcysteine (NAC), an anti-oxidant drug, has promising potential in the treatment of IPF. In the present systematic review and meta-analysis, the efficacy and safety of NAC for IPF were investigated. The following databases were comprehensively searched for relevant studies published until August 2018: Pubmed, Embase, Cochrane library, Chinese National Knowledge Infrastructure, Wangfang Database, VIP and the Chinese Biology Medical Database. A total of 21 controlled trials assessing the efficacy and safety of NAC therapy for IPF were identified and primary outcomes [forced vital capacity (FVC), adverse side effects] and secondary outcomes [diffusing capacity for carbon monoxide (DLCO) and its percentage predicted value (DLCO%), vital capacity (VC), partial arterial oxygen pressure (PaO_2), 6-min walking distance test and mortality] were extracted for the meta-analysis. The risk ratio and mean difference or standardized mean difference with 95% confidence interval were calculated using RevMan 5.3 software. Analysis of the pooled data revealed that, compared with control treatments (routine treatment or drugs other than anti-oxidants), NAC therapy reduced the decline in lung function, as indicated by the FVC and DLCO, and slowed the progression of the disease, as indicated by the PaO_2, while complications and mortality were similar. These results suggest good efficacy, tolerability and safety of the treatment. Furthermore, subgroup analysis revealed that combined therapy including NAC for IPF might be more effective than NAC monotherapy, while oral administration of NAC was safer than inhalation. In conclusion, the results of the present review and meta-analysis provide important information that may serve as a guide regarding NAC therapy for IPF in clinical practice.

Fowdar K, Chen H, He Z, Zhang J, Zhong X, Zhang J, Li M, Bai J. The effect of N-acetylcysteine on exacerbations of chronic obstructive pulmonary disease: A meta-analysis and systematic review. Heart & Lung. 2017 Mar 1;46(2):120-8.

Abstract

N-acetylcysteine (NAC) is an antioxidant and anti-inflammatory. Its effects on chronic obstructive pulmonary (COPD) outcomes, including exacerbation of and changes in lung function parameters, are controversial. To investigate the effects of NAC on COPD exacerbation and changes in lung function parameters in patients with COPD. A meta-analysis of randomized controlled trials retrieved from PubMed and Medline databases (12 trials; 2691 patients). High-dose [relative ratio (RR) = 0.90, 95% confidence interval (CI) = 0.82-0.996, P = 0.041] and low-dose (RR = 0.83, 95% CI = 0.69-0.99, P = 0.043) NAC reduced COPD exacerbation prevalence. Long-term (≥6 months), but not short-term, NAC reduced exacerbation prevalence (RR = 0.85, 95% CI = 0.74-0.98, P = 0.024). NAC did not affect exacerbation rate, forced expiratory volume in 1 s (FEV_1), forced vital capacity

(FVC), or inspiratory capacity (IC). Long-term NAC therapy may reduce risk of COPD exacerbation.

KEYWORDS: Chronic obstructive pulmonary disease; Effect; Exacerbation; Meta-analysis; N-acetylcysteine

Infection

Dinicola S, De Grazia S, Carlomagno G, Pintucci JP. N-acetylcysteine as powerful molecule to destroy bacterial biofilms. A systematic review. Eur Rev Med Pharmacol Sci. 2014 Oct 1;18(19):2942-8.

Abstract

OBJECTIVE: Biofilms are microbial communities consisting of bacteria, extremely capable to self-reproduce on biological surfaces, causing infections. Frequently, these biofilms are resistant to classical antibacterial treatments and host immune response. Thus, new adjuvant molecules are mandatory in clinical practice. N-acetylcysteine (NAC), a precursor to the antioxidant glutathione, has been investigated for its effectiveness both in inhibiting biofilm formation and in destroying developed biofilms. The aim of our study was to conduct a systematic literature review of clinical trials involving NAC as adjuvant treatment to eradicate pre-formed mature biofilms and to inhibit new biofilm production.
MATERIALS AND METHODS: A careful analysis of the Medline was conducted and eight studies were selected according to the following criteria: site of infection, kind of bacteria, design of the research, dose of the treatment, administration, biological effects and results. We fixed an arbitrary scale of scores from 0 (lowest score) to 5 (highest score) for each criterion and a threshold value of 3.
RESULTS: The studies analyzed, with score over 3, suggested a potential role for NAC as adjuvant molecule in the treatment of bacterial biofilms, with an excellent safety and efficacy profile. NAC, in combination with different antibiotics, significantly promoted their permeability to the deepest layers of the biofilm, overcoming the problem of the resistance to the classic antibacterial therapeutic approach.
CONCLUSIONS: Overall, these results are encouraging to a more widespread clinical use of NAC, as adjuvant therapy for microbial infections followed by biofilm settle, which may occur in several body districts, such as the vaginal cavity.

Cognition

Skvarc DR, Dean OM, Byrne LK, Gray L, Lane S, Lewis M, Fernandes BS, Berk M, Marriott A. The effect of N-acetylcysteine (NAC) on human cognition–A systematic review. Neuroscience & Biobehavioral Reviews. 2017 Jul 1; 78:44-56.

Abstract

Oxidative stress, neuroinflammation and neurogenesis are commonly implicated as cognitive modulators across a range of disorders. N-acetylcysteine (NAC) is a glutathione precursor with potent antioxidant, pro-neurogenesis and anti-inflammatory properties and a favourable safety profile. A systematic review of the literature specifically examining the effect of NAC administration on human cognition revealed twelve suitable articles for inclusion: four examining Alzheimer's disease; three examining healthy participants; two examining physical trauma; one examining bipolar disorder, one examining schizophrenia, and one examining ketamine-induced psychosis. Heterogeneity of studies, insufficiently powered studies, infrequency of cognition as a primary outcome, heterogeneous methodologies, formulations, co-administered treatments, administration regimes, and assessment confounded the drawing of firm conclusions. The available data suggested statistically significant cognitive improvements following NAC treatment, though the paucity of NAC-specific research makes it difficult to determine if this effect is meaningful. While NAC may have a positive cognitive effect in a variety of contexts; larger, targeted studies are warranted, specifically evaluating its role in other clinical disorders with cognitive sequelae resulting from oxidative stress and neuroinflammation.

Cardiometabolic Disease and Risk

Dludla PV, Dias SC, Obonye N, Johnson R, Louw J, Nkambule BB. A systematic review on the protective effect of N-acetyl cysteine against diabetes-associated cardiovascular complications. American Journal of Cardiovascular Drugs. 2018 Aug 1;18(4):283-98.

Abstract

INTRODUCTION: Heart failure is the leading cause of death in patients with diabetes. No treatment currently exists to specifically protect these patients at risk of developing cardiovascular complications. Accelerated oxidative stress-induced tissue damage due to persistent hyperglycemia is one of the major factors implicated in deteriorated cardiac function within a diabetic state. N-acetyl cysteine (NAC), through its enhanced capacity to endogenously synthesize glutathione, a potent antioxidant, has displayed abundant health-promoting properties and has a favorable safety profile.
OBJECTIVE: An increasing number of experimental studies have reported on the strong ameliorative properties of NAC. We systematically reviewed the data on the cardioprotective potential of this compound to provide an informative summary.
METHODS: Two independent reviewers systematically searched major databases, including PubMed, Cochrane Library, Google scholar, and Embase for available studies reporting on the ameliorative effects of NAC as a monotherapy or in combination with other therapies against diabetes-associated cardiovascular complications. We used the ARRIVE and JBI appraisal guidelines to assess the quality of individual studies included in the review. A meta-analysis could not be performed because the included studies were heterogeneous and data from randomized clinical trials were unavailable.
RESULTS: Most studies support the ameliorative potential of NAC against a number of diabetes-associated complications, including oxidative stress. We discuss future prospects, such as identification of additional molecular mechanisms implicated in diabetes-induced cardiac damage, and highlight limitations, such as insufficient studies reporting on the

comparative effect of NAC with common glucose-lowering therapies. Information on the comparative analysis of NAC, in terms of dose selection, administration mode, and its effect on different cardiovascular-related markers is important for translation into clinical studies. **CONCLUSIONS:** NAC exhibits strong potential for the protection of the diabetic heart at risk of myocardial infarction through inhibition of oxidative stress. The effect of NAC in preventing both ischemia and non-ischemic-associated cardiac damage is also of interest. Consistency in dose selection in most studies reported remains important in dose translation for clinical relevance.

Dludla PV, Nkambule BB, Dias SC, Johnson R. Cardioprotective potential of N-acetyl cysteine against hyperglycaemia-induced oxidative damage: a protocol for a systematic review. Syst Rev. 2017 May 12;6(1):96. doi: 10.1186/s13643-017-0493-8.

Abstract

BACKGROUND: Hyperglycaemia-induced oxidative damage is a well-established factor implicated in the development of diabetic cardiomyopathy (DCM) in diabetic individuals. Some of the well-known characteristics of DCM include increased myocardial left ventricular wall thickness and remodelling that result in reduced cardiac efficiency. To prevent this, an increasing number of pharmacological compounds such as N-acetyl cysteine (NAC) are explored for their antioxidant properties. A few studies have shown that NAC can ameliorate hyperglycaemia-induced oxidative damage within the heart. Hence, the objective of this review is to synthesise the available evidence pertaining to the cardioprotective role of NAC against hyperglycaemia-induced oxidative damage and thus prevent DCM.
METHODS: This systematic review protocol will be reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. We will perform a comprehensive search on major databases such as EMBASE, Cochrane Library, PubMed and Google scholar for original research articles published from January 1960 to March 2017. We will only report on literature that is available in English. Two authors will independently screen for eligible studies using pre-defined criteria, and data extraction will be done in duplicate. All discrepancies will be resolved by consensus or consultation of a third reviewer. The quality of studies will be checked using Cochrane Risk of Bias Assessment Tool and The Joanna Briggs Institute (JBI) Critical Appraisal tools for non-randomised experimental studies. Heterogeneity across studies will be assessed using the Cochrane Q statistic and the inconsistency index (I 2). We will use the random effects model to calculate a pooled estimate.
DISCUSSION: Although several studies have shown that NAC can ameliorate hyperglycaemia-induced oxidative damage within the heart, this systematic review will be the first pre-registered synthesis of data to identify the cardioprotective potential of NAC against hyperglycaemia-induced oxidative damage. This result will help guide future research evaluating the cardioprotective role of NAC against DCM and better identify possible mechanisms of action for NAC to prevent oxidative damage with a diabetic heart.
SYSTEMIC REVIEW REGISTRATION: PROSPERO CRD42017055851 .

KEYWORDS: Cardiac protection; Cardiomyopathy; Diabetes mellitus; N-acetyl cysteine; N-acetylcysteine; Oxidative stress

Waldron M, Patterson SD, Tallent J, Jeffries O. The effects of oral taurine on resting blood pressure in humans: a meta-analysis. Curr Hypertens Rep. 2018 Jul 13;20(9):81. doi: 10.1007/s11906-018-0881-z.

Abstract

PURPOSE OF REVIEW: The aims of this meta-analysis were to investigate the effects of orally administered isolated taurine on resting systolic blood pressure (SBP) and diastolic blood pressure (DBP) in humans.
RECENT FINDINGS: There is growing evidence that taurine deficiency is associated with hypertension and that oral supplementation can have antihypertensive effects in humans. However, these investigations have been conducted across a number of decades and populations and have not been collectively reviewed. A search was performed using various databases in May 2018 and later screened using search criteria for eligibility. There were seven peer-reviewed studies meeting the inclusion criteria, encompassing 103 participants of varying age and health statuses. Taurine ingestion reduced SBP (Hedges' g = - 0.70, 95% CI - 0.98 to - 0.41, P < 0.0001) and DBP (Hedges' g = - 0.62, 95% CI - 0.91 to - 0.34, P < 0.0001). These results translated to mean ~ 3 mmHg reductions in both SBP (range = 0-15 mmHg) and DBP (range = 0-7 mmHg) following a range of doses (1 to 6 g/day) and supplementation periods (1 day to 12 weeks), with no adverse events reported. These preliminary findings suggest that ingestion of taurine at the stated doses and supplementation periods can reduce blood pressure to a clinically relevant magnitude, without any adverse side effects. Future studies are needed to establish the effects of oral taurine supplementation on targeted pathologies and the optimal supplementation doses and periods.

KEYWORDS: Hypertension; Oral taurine; Taurine deficiency

Polycystic Ovarian Syndrome

Thakker D, Raval A, Patel I, Walia R. N-acetylcysteine for polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled clinical trials. Obstetrics and gynecology international. 2015;2015.

Abstract

OBJECTIVE: To review the benefits and harms of N-acetylcysteine (NAC) in women with polycystic ovary syndrome (PCOS).
METHOD: Literature search was conducted using the bibliographic databases, MEDLINE (Ovid), CINAHL, EMBASE, Scopus, PsyInfo, and PROQUEST (from inception to September 2013) for the studies on women with PCOS receiving NAC.
RESULTS: Eight studies with a total of 910 women with PCOS were randomized to NAC or other treatments/placebo. There were high risk of selection, performance, and attrition bias in two studies and high risk of reporting bias in four studies. Women with NAC had

higher odds of having a live birth, getting pregnant, and ovulation as compared to placebo. However, women with NAC were less likely to have pregnancy or ovulation as compared to metformin. There was no significant difference in rates of the miscarriage, menstrual regulation, acne, hirsutism, and adverse events, or change in body mass index, testosterone, and insulin levels with NAC as compared to placebo.
CONCLUSIONS: NAC showed significant improvement in pregnancy and ovulation rate as compared to placebo. The findings need further confirmation in well-designed randomized controlled trials to examine clinical outcomes such as live birth rate in longer follow-up periods. Systematic review registration number is CRD42012001902.

Neurological Disorders

Li S, Li Q, Li Y, Li L, Tian H, Sun X. Acetyl-L-carnitine in the treatment of peripheral neuropathic pain: a systematic review and meta-analysis of randomized controlled trials. PLoS One. 2015 Mar 9;10(3):e0119479. doi: 10.1371/journal.pone.0119479.

Abstract

OBJECTIVE: Acetyl-L-carnitine (ALC), a constructive molecule in fatty acid metabolism, is an agent potentially effective for treating peripheral neuropathic pain (PNP). Its effect, however, remains uncertain. We aimed to access the efficacy and safety of ALC for the treatment of patients with PNP.
METHODS: We searched MEDLINE (1996-2014), EMBase (1974-2014), and CENTRAL (May 2014) up to June 27, 2014 for randomized controlled trials (RCTs) comparing ALC with placebo or other active medications in diabetic and non-diabetic PNP patients that reported the change of pain using visual analogue scale (VAS). Mean difference (MD) and 95% confidence interval (CI) were used for pooling continuous data.
RESULTS: Four RCTs comparing ALC with placebo and reporting in three articles (n = 523) were included. Compared with placebo, ALC significantly reduced VAS scores of PNP patients (MD of VAS, 1.20; 95% CI, 0.68-1.72, P <0.00001). In the subgroup analysis, the effect of ALC on VAS was similar in different administration routes (intramuscular-oral sequential subgroup: MD, 1.19; 95% CI, 0.34-2.04, P = 0.006; oral only subgroup: pooled MD, 1.15; 95%CI, 0.33-1.96, P = 0.006), and ALC appeared more effective in diabetic PNP patients than non-diabetic PNP patients (diabetic subgroup: MD, 1.47; 95%CI, 1.06-1.87, P <0.00001; non-diabetic subgroup: MD, 0.71; 95% CI, -0.01-1.43, P = 0.05). No severe adverse events were reported related to ALC. The common adverse events were pain, headache, paraesthesia, hyperesthesia, retching, biliary colic, and gastrointestinal disorders. The rates of total adverse events were similar in ALC and control group.
CONCLUSION: The current evidence suggests that ALC has a moderate effect in reducing pain measured on VAS in PNP patients with acceptable safety. Larger trials with longer follow-up, however, are warranted to establish the effects.

Cancer Risk and Support

Jolfaie NR, Mirzaie S, Ghiasvand R, Askari G, Miraghajani M. The effect of glutamine intake on complications of colorectal and colon cancer treatment: A systematic review. J Res Med Sci. 2015 Sep;20(9):910-8. doi: 10.4103/1735-1995.170634.

Abstract

BACKGROUND: Improvement in complications of antitumor agents and surgery is important to enhance life quality and survival among patients with colon and colorectal cancer. It has been reported that some dietary components such as glutamine (Gln) have beneficial effects on these complications of cancer therapies. However, the results of studies are inconsistent in this area. We performed a review on randomized controlled trials (RCTs) evaluating the effects of Gln intake on complications related to therapeutic strategies of the colon and colorectal cancer.
MATERIALS AND METHODS: A systematic search was conducted in PubMed, Google Scholar, Cochrane Library, and SID databases to find the relevant literature, published before July 2015.
RESULTS: Nine RCTs of 217 screened articles were included in this systematic review. The results of the present review suggested that Gln intake among colon and colorectal cancer patients could reduce some complications induced by chemotherapy such as gut mucositis and diarrhea and improve nitrogen balance, immune system and wound healing after surgery, whereas benefits role of Gln on radiochemotherapy side effects were not provided.
CONCLUSION: The role of Gln intake on some improvement of complications induced by cancer therapeutic methods and shorten the length of hospital stay may be promising and one that is worthy of further exploration.

Leung HW, Chan AL. Glutamine in alleviation of radiation-induced severe oral mucositis: a meta-analysis. Nutr Cancer. 2016 Jul;68(5):734-42. doi: 10.1080/01635581.2016.1159700.

Abstract

The aim of this meta-analysis was to assess the effectiveness of glutamine to treat severe mucositis induced by radiation therapy in patients with head and neck cancer. We undertook electronic searches of PubMed (1990 to January 2015), Embase (1990 to January 2015), and the Cochrane Library (2013, Issue 2) to identify relevant studies. We included randomized controlled trials of glutamine to alleviate oral mucositis (OM) in patients with head and neck cancer who received radiotherapy. Information regarding methods, patients, results, and risk of bias was independently extracted by two authors. Statistical analyses were conducted to calculate the odds ratio and 95% confidence intervals (95%CIs) using fixed-effect models. We identified five clinical studies that included 234 patients with head and neck cancer. All studies were assessed as being at low risk of bias in most items of six domains. In this meta-analysis, glutamine treatment showed a statistically significant benefit with respect to reducing the risk and severity of OM induced by radiotherapy compared to either placebo or no treatment (risk ratio 0.17, 95%CI 0.06-

0.47). Overall, glutamine significantly reduces the risk and severity of OM during radiotherapy or chemotherapy. Further prospective and large trials are required to support the findings.

Papanikolopoulou A1, Syrigos KN, Drakoulis N. The role of glutamine supplementation in thoracic and upper aerodigestive malignancies. Nutr Cancer. 2015;67(2):231-7. doi: 10.1080/01635581.2015.990572.

Abstract

In cancer patients, marked glutamine (gln) depletion develops over time. Host tissues (epithelial cells and lymphocytes) that depend upon adequate stores of gln for optimal functioning can be negatively influenced. In addition, radiation and/or chemotherapy cause normal tissues damage that might be enhanced by this depletion effect. The present review evaluates in vivo clinical data about the potential beneficial role of gln administration in the prevention of host tissue toxicity, in a patient group with thoracic and upper aerodigestive malignancies (T&UAM) during cancer treatment. Publications were identified in a systematic review of MEDLINE Database from the last 2 decades (1994-2014) using key search terms and through manual searches. Overall, 13 clinical studies (9 oral/4 parenteral) evaluated the safety and tolerance of gln supply, showing a beneficial effect in the grade, duration of mucositis and esophagitis, decreased gut permeability, and weight loss. Only 1 Phase 1 clinical trial had negative results because the chemo-radiotherapy combined treatment was not feasible. The use of oral gln may especially have an important role in the prevention of acute radiation toxicities, the weight loss and the need for analgesics in patients with T&UAM, especially if the treatment plan includes combined modality therapy with chemo-radiation.

Sayles C, Hickerson SC, Bhat RR, Hall J, Garey KW, Trivedi MV. Oral glutamine in preventing treatment-related mucositis in adult patients with cancer: a systematic review. Nutr Clin Pract. 2016 Apr;31(2):171-9. doi: 10.1177/0884533615611857.

Abstract

BACKGROUND: Breakdown of the mucosal barrier resulting in mucositis is a common adverse event in patients with cancer receiving chemotherapy and radiation. Many studies have evaluated the use of oral glutamine to prevent mucositis in these settings, but current guidelines make no recommendations with regard to its use. Our objective was to systematically review the evidence for the use of oral glutamine in preventing mucositis in adult patients with cancer undergoing chemotherapy and/or radiation.
MATERIALS AND METHODS: A systematic search of English-language literature was done via MEDLINE using the search terms glutamine, cancer, and mucositis or esophagitis or stomatitis. Fifteen studies conducted in adult patients with cancer receiving chemotherapy and/or radiation comparing single-agent oral glutamine with control were

identified.
RESULTS: Oral glutamine was shown to be effective in 11 of the 15 studies included in the systematic review. It significantly reduced the incidence of grade 2, 3, or 4 mucositis and/or reduced weight loss as well as the duration, time of onset, and/or maximum grade of mucositis. The most common dosing regimen was 30 g/d in 3 divided doses, with other regimens ranging from 7.5-24 g/d. Rates of nausea, vomiting, dry mouth, and anorexia were similar in the glutamine and control groups.
CONCLUSION: In summary, the favorable efficacy and low toxicity of oral glutamine observed in clinical trials we reviewed provide a strong rationale for large randomized placebo-controlled studies to further evaluate its efficacy in preventing mucositis in patients with cancer receiving chemotherapy and/or radiation.

RANDOMISED CONTROLLED TRIALS

Cardiometabolic Disease and Risk

Laviano A1, Molfino A1, Lacaria MT1, Canelli A1, De Leo S1, Preziosa I1, et al. Glutamine supplementation favors weight loss in nondieting obese female patients. A pilot study. Eur J Clin Nutr. 2014 Nov;68(11):1264-6. doi: 10.1038/ejcn.2014.184.

Abstract

Glutamine supplementation improves insulin sensitivity in critically ill patients, and prevents obesity in animals fed a high-fat diet. We hypothesized that glutamine supplementation favors weight loss in humans. Obese and overweight female patients (n=6) were enrolled in a pilot, cross-over study. After recording anthropometric (that is, body weight, waist circumference) and metabolic (that is, glycemia, insulinemia, homeostatic model of insulin resistance (HOMA-IR)) characteristics, patients were randomly assigned to 4-week supplementation with glutamine or isonitrogenous protein supplement (0.5 g/KgBW/day). During supplementation, patients did not change their dietary habits nor lifestyle. At the end, anthropometric and metabolic features were assessed, and after 2 weeks of washout, patients were switched to the other supplement for 4 weeks. Body weight and waist circumference significantly declined only after glutamine supplementation (85.0±10.4 Kg vs 82.2±10.1 Kg, and 102.7±2.0 cm vs 98.9±2.9 cm, respectively; P=0.01). Insulinemia and HOMA-IR declined by 20% after glutamine, but not significantly so. This pilot study shows that glutamine is safe and effective in favoring weight loss and possibly enhancing glucose metabolism.

Li S, Chen X, Li Q, Du J, Liu Z, Peng Y, et al. Effects of acetyl-L-carnitine and methylcobalamin for diabetic peripheral neuropathy: A multicenter, randomized, double-blind, controlled trial. J Diabetes Investig. 2016 Sep;7(5):777-85. doi: 10.1111/jdi.12493.

Abstract

AIMS/INTRODUCTION: To assess the efficacy and safety of acetyl-L-carnitine (ALC) on diabetic peripheral neuropathy compared with methylcobalamin (MC).
MATERIALS AND METHODS: This was a multicenter, randomized, parallel-group, double-blind, double-dummy, positive-controlled, non-inferior phase II clinical trial. Diabetic patients with abnormal nerve conduction test results were randomized in a 1:1 ratio to receive oral ALC 500 mg t.i.d. or MC 0.5 mg t.i.d. for 24 weeks. The neuropathy symptom score, neuropathy disability score and neurophysiological parameters were measured during follow up.
RESULTS: A total of 232 patients were randomized (ALC n = 117, MC n = 115), 88% of which completed the trial. At week 24, patients from both groups had significant reductions in both neuropathy symptom score and neuropathy disability score with no significant difference between two groups (neuropathy symptom score reduction: ALC vs MC 2.35 ± 2.23, P < 0.0001 vs 2.11 ± 2.48, P < 0.0001, intergroup P = 0.38; neuropathy disability score reduction ALC vs MC 1.66 ± 1.90, P < 0.0001 vs 1.35 ± 1.65, P < 0.0001, intergroup P = 0.23). Neurophysiological parameters were also improved in both groups. No significant difference was found between groups in the development of adverse events.
CONCLUSIONS: ALC is as effective as MC in improving clinical symptoms and neurophysiological parameters for patients with diabetic peripheral neuropathy over a 24-week period with good tolerance.
KEYWORDS: Acetyl-L-carnitine; Diabetic peripheral neuropathy; Methylcobalamin

Sun Q, Wang B, Li Y, Sun F, Li P, Xia W, et al. Taurine Supplementation Lowers Blood Pressure and Improves Vascular Function in Prehypertension: Randomized, Double-Blind, Placebo-Controlled Study. Hypertension. 2016 Mar;67(3):541-9. doi: 10.1161/HYPERTENSIONAHA.115.06624.

Abstract

Taurine, the most abundant, semi essential sulfur-containing amino acid, is well known to lower blood pressure (BP) in hypertensive animal models. However, no rigorous clinical trial has validated whether this beneficial effect of taurine occurs in human hypertension or prehypertension, a key stage in the development of hypertension. In this randomized, double-blind, placebo-controlled study, we assessed the effects of taurine intervention on BP and vascular function in prehypertension. We randomly assigned 120 eligible prehypertensive individuals to receive either taurine supplementation (1.6 g per day) or a placebo for 12 weeks. Taurine supplementation significantly decreased the clinic and 24-hour ambulatory BPs, especially in those with high-normal BP. Mean clinic systolic BP reduction for taurine/placebo was 7.2/2.6 mm Hg, and diastolic BP was 4.7/1.3 mm Hg. Mean ambulatory systolic BP reduction for taurine/placebo was 3.8/0.3 mm Hg, and diastolic BP was 3.5/0.6 mm Hg. In addition, taurine supplementation significantly improved endothelium-dependent and endothelium-independent vasodilation and increased plasma H2S and taurine concentrations. Furthermore, changes in BP were negatively correlated with both the plasma H2S and taurine levels in taurine-treated prehypertensive individuals. To further elucidate the hypotensive mechanism, experimental studies were performed both in vivo and in vitro. The results showed that taurine treatment upregulated the expression of hydrogen sulfide-synthesizing enzymes and reduced agonist-induced vascular reactivity

through the inhibition of transient receptor potential channel subtype 3-mediated calcium influx in human and mouse mesenteric arteries. In conclusion, the antihypertensive effect of chronic taurine supplementation shows promise in the treatment of prehypertension through improvement of vascular function.
KEYWORDS: blood pressure; hydrogen sulfide; prehypertension; taurine; transient receptor potential channels

Cognition

van de Rest O, Bloemendaal M, de Heus R, Aarts E. Dose-dependent effects of oral tyrosine administration on plasma tyrosine levels and cognition in aging. Nutrients. 2017 Nov 23;9(12). pii: E1279.

Abstract

The effects of tyrosine on plasma response and cognition in aging are unknown. We assessed the dose-dependent response to tyrosine administration in older adults in both plasma tyrosine concentrations and working memory performance. In this double blind randomized cross-over trial 17 older adults (aged 60-75 years) received a single administration of 100, 150, or 200 mg/kg body weight of tyrosine. For comparison, 17 young adults (aged 18-35 years) received a dose of 150 mg/kg body weight of tyrosine. Tyrosine plasma concentrations were determined before and 90, 120, 150, 180, 210, and 240 min after tyrosine intake. Working memory was assessed using the N-back task at 90 min after tyrosine administration. Older adults showed a dose-dependent increase in plasma tyrosine concentrations ($p < 0.001$), and the plasma response was higher than for young adults with the same dose ($p < 0.001$). Load-dependent working memory performance decreased with higher doses of tyrosine ($p = 0.048$), especially in older adults with greater dose-dependent plasma tyrosine responses ($p = 0.035$). Our results show an age-related increase in plasma tyrosine response, which was associated with a dose-dependent decline in cognitive functioning in older adults.
KEYWORDS: aging; catecholamines; dopamine; dose-response; plasma amino acids; tyrosine; working memory

Neuropsychiatric Disorders and Addiction

Nesic J, Duka T. Effects of stress and dietary tryptophan enhancement on craving for alcohol in binge and non-binge heavy drinkers. Behav Pharmacol. 2014 Sep;25(5-6):503-17. doi: 10.1097/FBP.0000000000000067.

Abstract

Stress is known to play an important role in alcohol abuse, whereas binge drinking may increase individuals' susceptibility to the development of alcohol dependence. We set out to investigate whether binge drinkers (BDs) or non-BDs (NBDs) are at a greater risk of an increase in their desire for alcohol following experimental stress induction (modified Trier Social Stress Test; Experiment 1) and to explore the biological mechanisms underlying

such an effect (Experiment 2). Preclinical evidence suggests that serotonin may mediate stress-induced reinstatement of alcohol intake. We therefore tested whether dietary tryptophan (TRP) enhancement would modulate stress-induced desire for alcohol and whether it would affect the two populations (BD/NBD) differently. In Experiment 1 (14 NBDs, 10 BDs; mean weekly alcohol intake 50.64 U), stress induction selectively increased strong desire for alcohol compared with the nonstressful condition in BDs. Throughout the experiment, BDs reported greater negative reinforcement type of craving than NBDs, but also a higher expectancy of alcohol-induced negative effects. In Experiment 2, 41 participants (22 NBDs, 19 BDs; mean alcohol intake 38.81 U) were given either the TRP-rich (TRP+; 9 BDs, 11 NBD) or the control (CTR; 10 BD, 11 NBD) diet before undergoing stress induction. In BDs, the TRP+ diet prevented the stress-induced increase in strong desire that was observed in individuals receiving the CTR diet. In NBDs, the TRP+ diet appeared to facilitate an increase in strong desire. These findings suggest that BDs may indeed be at a greater risk than NBDs of an increase in their craving for alcohol when stressed. Furthermore, whereas enhancement of 5-hydroxytryptamine function may moderate the impact of stress on craving in BDs, it seems to facilitate stress-induced craving in NBDs, suggesting that the serotonergic system may be differentially involved depending on individual binge drinking status.

Paydary K, Akamaloo A, Ahmadipour A, Pishgar F, Emamzadehfard S, Akhondzadeh S. N-acetylcysteine augmentation therapy for moderate-to-severe obsessive-compulsive disorder: randomized, double-blind, placebo-controlled trial. J Clin Pharm Ther. 2016 Apr;41(2):214-9. doi: 10.1111/jcpt.12370.

Abstract

WHAT IS KNOWN AND OBJECTIVE: N-acetylcysteine (NAC) has been proposed as a potential therapy for obsessive-compulsive disorder (OCD) as it may regulate the exchange of glutamate and prevent its pre-oxidant effects. The aim of the present double-blind, placebo-controlled trial was to assess the efficacy and tolerability of NAC augmentation in moderate-to-severe (OCD) treatment.
METHODS: In this randomized, double-blind, two-centre, placebo-controlled, 10-week trial, patients with moderate-to-severe OCD were enrolled. Patients were randomized into two parallel groups to receive fluvoxamine (200 mg daily) plus placebo or fluvoxamine (200 mg daily) plus NAC (2000 mg daily). A total of 44 patients (22 in each group) were visited to evaluate response to therapy using the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) at baseline, and at weeks 4, 8 and 10. Side effects were recorded using predesigned checklists upon each visit.
RESULTS AND DISCUSSION: Repeated-measures ANOVA showed a significant effect for time × treatment interaction (Greenhouse-Geisser corrected: F = 5·14, d.f. = 1·64, P = 0·012) in the Y-BOCS total score and a significant effect for time × treatment interaction (Greenhouse-Geisser corrected: F = 5·44, d.f. = 1·54, P = 0·011) in the Y-BOCS obsession subscale between the two groups.
WHAT IS NEW AND CONCLUSION: Our results showed that NAC might be effective as an augmentative agent in the treatment of moderate-to-severe OCD.

TRIAL REGISTRATION: Iranian Registry of Clinical Trials (www.irct.ir): IRCT201405271556N60.
KEYWORDS: N-acetylcysteine; augmentative therapy; obsessive-compulsive disorder; randomized controlled trial

Gastrointestinal Disorders

Zhou Q, Verne ML, Fields JZ, Lefante JJ, Basra S, Salameh H, et al. Randomised placebo-controlled trial of dietary glutamine supplements for postinfectious irritable bowel syndrome. Gut. 2019 Jun;68(6):996-1002. doi: 10.1136/gutjnl-2017-315136.

Abstract

BACKGROUND: More effective treatments are needed for patients with postinfectious, diarrhoea-predominant, irritable bowel syndrome (IBS-D). Accordingly, we conducted a randomised, double-blind, placebo-controlled, 8-week-long trial to assess the efficacy and safety of oral glutamine therapy in patients who developed IBS-D with increased intestinal permeability following an enteric infection.
METHODS: Eligible adults were randomised to glutamine (5 g/t.i.d.) or placebo for 8 weeks. The primary end point was a reduction of ≥50 points on the Irritable Bowel Syndrome Severity Scoring System (IBS-SS). Secondary endpoints included: raw IBS-SS scores, changes in daily bowel movement frequency, stool form (Bristol Stool Scale) and intestinal permeability.
RESULTS: Fifty-four glutamine and 52 placebo subjects completed the 8-week study. The primary endpoint occurred in 43 (79.6%) in the glutamine group and 3 (5.8%) in the placebo group (a 14-fold difference). Glutamine also reduced all secondary endpoint means: IBS-SS score at 8 weeks (301 vs 181, p<0.0001), daily bowel movement frequency (5.4 vs 2.9±1.0, p<0.0001), Bristol Stool Scale (6.5 vs 3.9, p<0.0001) and intestinal permeability (0.11 vs 0.05; p<0.0001). 'Intestinal hyperpermeability' (elevated urinary lactulose/mannitol ratios) was normalised in the glutamine but not the control group. Adverse events and rates of study-drug discontinuation were low and similar in the two groups. No serious adverse events were observed.
CONCLUSIONS: In patients with IBS-D with intestinal hyperpermeability following an enteric infection, oral dietary glutamine supplements dramatically and safely reduced all major IBS-related endpoints. Large randomised clinical trials (RCTs) should now be done to validate these findings, assess quality of life benefits and explore pharmacological mechanisms.
TRIAL REGISTRATION NUMBER: NCT01414244; Results.
KEYWORDS: diarrhoea; enteric infections; intestinal permeability; irritable bowel syndrome

Reproductive Disorders and Fertility

Cheraghi E, Mehranjani MS, Shariatzadeh MA, Esfahani MH, Ebrahimi Z. N-Acetylcysteine improves oocyte and embryo quality in polycystic ovary syndrome patients undergoing intracytoplasmic sperm injection: an

alternative to metformin. Reprod Fertil Dev. 2016 Apr;28(6):723-31. doi: 10.1071/RD14182.

Abstract

Polycystic ovary syndrome (PCOS) is associated with low-quality oocytes. The aim of the present study was to investigate the effects of metformin (MET), N-acetylcysteine (NAC) and their combination on follicular fluid parameters, oocytes and embryo quality in PCOS patients. A prospective randomised placebo-controlled pilot study on 60 Iranian women with PCOS (aged 25-35 years) undergoing intracytoplasmic sperm injection (ICSI) was designed. Women were divided into four groups (n=15 in each): (1) an MET, administered 1500mg day(-1) MET; (2) an NAC group, administered 1800mg day(-1) NAC; (3) an NAC + MET group; and (4) a placebo group. Drugs were administered from the 3rd day of previous cycle until the day of oocyte aspiration (6 weeks treatment in total). Data were analysed by one-way ANOVA, with significance set at $P<0.05$. The number of immature and abnormal oocytes decreased significantly in the NAC compared with placebo group, with a concomitant increase in the number of good-quality embryos in the NAC group ($P<0.05$). Malondialdehyde levels decreased significantly in the NAC and NAC + MET groups compared with the placebo-treated group ($P<0.02$). In addition, there were significant decreases in leptin levels in the NAC, MET and NAC + MET groups compared with the placebo group ($P<0.001$). Insulin and LH levels were significantly lower in the MET and NAC groups compared with the placebo-treated group ($P<0.02$). We concluded that NAC improves oocyte and embryo quality and could be administered as an alternative to MET.

Fernandez-Pareja A, Hernandez-Blanco E, Perez-Maceda JM, Rubio VJ, Palazuelos JH, Dalmau JM. Prevention of Osteoporosis Four-Year Follow-Up of a Cohort of Postmenopausal Women Treated with an Ossein-Hydroxyapatite Compound. Clin Drug Invest. 2007; 27 (4):227-232.

Javanmanesh, Kashanian, Rahimi, Sheikhansari. A comparison between the effects of metformin and N-acetyl cysteine (NAC) on some metabolic and endocrine characteristics of women with polycystic ovary syndrome. Gynecol Endocrinol. 2016;32(4):285-9. doi: 10.3109/09513590.2015.1115974.

Abstract

OBJECTIVE: To compare N-acetyl cysteine (NAC) and metformin on polycystic ovary syndrome (PCOS).
METHOD: Study was performed as a randomized double-blind clinical trial on women with diagnosis of PCOS without additional complications. In one group, oral NAC 600 mg, three times a day and in the other group, 500 mg oral metformin, three times a day were prescribed. Duration of treatment was 24 weeks, and after finishing this period of treatment, fasting blood glucose (FBS) and insulin, lipid profile and Homeostasis Model Assessment (HOMA) index were measured (all the blood samples were taken while fasting) and were compared in the two groups.
RESULTS: Forty-six women in NAC group and 48 women in metformin group finished the

study. The two groups did not show significant difference according to age, body mass index (BMI) of more than 30; mean BMI, AUB, FBS, fasting blood insulin, lipid profile and HOMA index before treatment. After 24 weeks of treatment; BMI >30 [17 (35.4%) versus 7 (15.2%), p = 0.033], mean BMI [(28.36 ± 2.27) versus (27.11 ± 3.55), p = 0.44], number of women with the complain of abnormal uterine bleeding (AUB) [24 (50%) versus 13 (28.3%), p = 0.037], FBS [(90.02 ± 6.24) versus (86.61 ± 7.81), p = 0.021], fasting insulin (10.40 ± 2.64 versus 8.89 ± 2.20, p = 0.004), HOMA Index (2.09 ± 0.69 versus 1.71 ± 0.45, p = 0.001), low density lipoprotein (LDL) (141.83 ± 26.98 versus 127.89 ± 28.70, p = 0.017) were less in NAC group. Triglyceride (TG) and total cholesterol did not show significant difference between the two groups after treatment. High-density lipoprotein (HDL) was higher in NAC group.
CONCLUSION: NAC can improve lipid profile and fasting blood sugar (FBS) and fasting blood insulin better than metformin.
KEYWORDS: Abnormal uterine bleeding; BMI; N-acetyl cysteine; fasting blood insulin; fasting blood sugar; insulin resistance; lipid profile; metformin; polycystic ovary syndrome

Neurological Disorders and Pain Syndromes

Leombruni P, Miniotti M, Colonna F, Sica C, Castelli L, Bruzzone M, et al. A randomised controlled trial comparing duloxetine and acetyl L-carnitine in fibromyalgic patients: preliminary data. Clin Exp Rheumatol. 2015 Jan-Feb;33(1 Suppl 88):S82-5.

Abstract

OBJECTIVES: Fibromyalgia syndrome (FMS) is a chronic disorder characterised by widespread musculoskeletal pain, troubled sleep, disturbed mood, and fatigue. Recently published reviews have demonstrated that it is influenced by various psychological aspects, and antidepressants are now considered the treatment of choice for most patients. The aim of this randomised controlled trial was to compare the effects of duloxetine and acetyl L-carnitine on pain, depression, anxiety and well-being in FMS patients.
METHODS: Sixty-five female outpatients with FMS diagnosed by a rheumatologist were recruited between January 2011 and May 2012, and randomised to receive duloxetine 60 mg/day or acetyl L-carnitine 1500 mg/day (500 mg t.i.d.). Drug efficacy and side effects were assessed by the same psychiatrist at baseline, and four and 12 weeks later.
RESULTS: Both drugs led to a general clinical improvement, with positive effects on pain and depressive symptoms; but neither induced a significant improvement in anxiety. Both drugs had a positive effect on the physical component of the quality of life, but only duloxetine improved the psychological component.
CONCLUSIONS: Although they need to be confirmed by further studies, these preliminary findings confirm the efficacy of duloxetine, and suggest that acetyl L-carnitine is also efficacious in improving depressive symptoms, pain, and the quality of life of FMS patients.

MAGNESIUM

OVERVIEW

Hsiao-Yean Chiu, Tu-Hsueh Yeh, Yin-Cheng Huang, Pin-Yuan Chen. Effects of Intravenous and Oral Magnesium on Reducing Migraine: A Meta-analysis of Randomized Controlled Trials. Pain Physician 2016; 19:E97-E112

Abstract

BACKGROUND: Migraine attack has been associated with magnesium deficiency. Previous studies investigating the effect of intravenous and oral magnesium on acute migraine attacks and the prevention of migraine have produced equivocal findings.
OBJECTIVE: To evaluate the effects of intravenous magnesium on acute migraine attacks and oral magnesium supplements on migraine prophylaxis.
STUDY DESIGN: A meta-analysis of randomized controlled trials (RCTs). Setting: Electronic databases, namely EMBASE, PubMed, the Wanfang Data Chinese Database, and the China Knowledge Resource Integrated Database were searched from inception to February 24, 2015.
METHODS: This review was conducted according to the guidelines of the PRISMA. Only RCTs evaluating the effects of intravenous or oral magnesium on migraine compared with a control group were included.
RESULTS: A total of 21 studies were included. Of which, 11 studies investigated the effects of intravenous magnesium on acute migraine (948 participants) and 10 examined the effects of oral magnesium on migraine prophylaxis (789 participants). Intravenous magnesium significantly relieved acute migraine within 15 – 45 minutes, 120 minutes, and 24 hours after the initial infusion (Odd ratios [ORs] = 0.23, 0.20, and 0.25, respectively). Oral magnesium significantly alleviated the frequency and intensity of migraine (ORs = 0.20 and 0.27).
LIMITATIONS: Some of the included studies did not adopt adequate randomization methods.
CONCLUSIONS: Intravenous magnesium reduces acute migraine attacks within 15 – 45 minutes, 120 minutes, and 24 hours after the initial infusion and oral magnesium alleviates the frequency and intensity of migraine. Intravenous and oral magnesium should be adapted as parts of multimodal approach to reduce migraine.

KEY WORDS: Magnesium, migraine, meta-analysis

Von Luckner A, Riederer F. Magnesium in Migraine Prophylaxis - Is There an Evidence-Based Rationale? Headache, Feb2018; 58(2): 199-209. DOI: http://dx.doi.org/10.1111/head.13217

Abstract

OBJECTIVE: The primary objective was to systematically evaluate the existing evidence base on magnesium in migraine prophylaxis.
METHODS: The search for clinical trials published from 1990 to 2016 was separately conducted by AvL and FR using standard search terms as well as MeSh terms on PubMed

and EMBASE. Randomized, double-blind, placebo-controlled trials investigating prophylactic magnesium administration in migraineurs aged 18-65 were considered eligible. In a mutual effort, the studies found were sorted and analyzed under consideration of the guidelines for controlled trials for drugs in migraine by the International Headache Society and using predefined eligibility criteria. The resulting clinical trials were jointly analyzed by FR and AvL applying the evidence classification scheme by the American Academy of Neurology and the Cochrane bias tool to assess the evidence-base. In accordance with the guidelines for controlled trials, the number of migraine days and number of migraine attacks were chosen as primary efficacy parameters. The present review was not registered. Results: Out of 204 search results, five clinical trials fulfilling the selection procedure were found. One out of two Class I evidence trials showed a significant reduction of the number of migraine attacks compared with placebo, while two out of three Class III trials evinced a statistically significant reduction of the primary efficacy parameters compared with placebo. Conclusion: This systematic review provides Grade C (possibly effective) evidence for prevention of migraine with magnesium. Prophylactic treatment of migraine by means of high levels of magnesium dicitrate (600 mg) seems to be a safe and cost efficient strategy in clinical use.

Xin Fang, Hedong Han, Mei Li, Chun Liang, Zhongjie Fan, Aaseth Jan, Jia He, Montgomery Scott, Yang Cao. Dose-Response Relationship between Dietary Magnesium Intake and Risk of Type 2 Diabetes Mellitus: A Systematic Review and Meta Regression Analysis of Prospective Cohort Studies. Nutrients, Nov.2016; 8(11):739.

Abstract

The epidemiological evidence for a dose-response relationship between magnesium intake and risk of type 2 diabetes mellitus (T2D) is sparse. The aim of the study was to summarize the evidence for the association of dietary magnesium intake with risk of T2D and evaluate the dose-response relationship. We conducted a systematic review and meta-analysis of prospective cohort studies that reported dietary magnesium intake and risk of incident T2D. We identified relevant studies by searching major scientific literature databases and grey literature resources from their inception to February 2016. We included cohort studies that provided risk ratios, i.e., relative risks (RRs), odds ratios (ORs) or hazard ratios (HRs), for T2D. Linear dose-response relationships were assessed using random-effects meta-regression. Potential nonlinear associations were evaluated using restricted cubic splines. A total of 25 studies met the eligibility criteria. These studies comprised 637,922 individuals including 26,828 with a T2D diagnosis. Compared with the lowest magnesium consumption group in the population, the risk of T2D was reduced by 17% across all the studies; 19% in women and 16% in men. A statistically significant linear dose-response relationship was found between incremental magnesium intake and T2D risk. After adjusting for age and body mass index, the risk of T2D incidence was reduced by 8%-13% for per 100 mg/day increment in dietary magnesium intake. There was no evidence to support a nonlinear dose-response relationship between dietary magnesium intake and T2D risk. The combined data supports a role for magnesium in reducing risk of T2D, with a statistically significant linear dose-response pattern within the reference dose range of dietary intake among Asian

and US populations. The evidence from Europe and black people is limited and more prospective studies are needed for the two subgroups.

RANDOMISED CONTROLLED TRIALS

Guerrero-Romero F, Simental-Mendía LE, Hernández-Ronquillo G, Rodriguez-Morán M. Oral magnesium supplementation improves glycaemic status in subjects with prediabetes and hypomagnesaemia: A double-blind placebo-controlled randomized trial. 2015; DOI.org/10.1016/j.diabet.2015.03.010

Abstract

This study evaluated the efficacy of oral magnesium supplementation in the reduction of plasma glucose levels in adults with prediabetes and hypomagnesaemia.

METHODS: A total of 116 men and non-pregnant women, aged 30 to 65 years with hypomagnesaemia and newly diagnosed with prediabetes, were enrolled into a randomized double-blind placebo-controlled trial to receive either 30 mL of $MgCl_2$5% solution (equivalent to 382 mg of magnesium) or an inert placebo solution once daily for four months. The primary trial endpoint was the efficacy of magnesium supplementation in reducing plasma glucose levels.

RESULTS: At baseline, there were no significant statistical differences in terms of anthropometric and biochemical variables between individuals in the supplement and placebo groups. At the end of follow-up, fasting (86.9 ± 7.9 and 98.3 ± 4.6 mg/dL, respectively; $P = 0.004$) and post-load glucose (124.7 ± 33.4 and 136.7 ± 23.9 mg/dL, respectively; $P = 0.03$) levels, HOMA-IR indices (2.85 ± 1.0 and 4.1 ± 2.7, respectively; $P = 0.04$) and triglycerides (166.4 ± 90.6 and 227.0 ± 89.7, respectively; $P = 0.009$) were significantly decreased, whereas HDL cholesterol (45.6 ± 10.9 and 46.8 ± 9.2 mg/dL, respectively; $P = 0.04$) and serum magnesium (1.96 ± 0.27 and 1.60 ± 0.26 mg/dL, respectively; $P = 0.005$) levels were significantly increased in those taking $MgCl_2$compared with the controls. A total of 34 (29.4%) people improved their glucose status (50.8% and 7.0% in the magnesium and placebo groups, respectively; $P < 0.0005$).

CONCLUSION: Our results show that magnesium supplementation reduces plasma glucose levels, and improves the glycaemic status of adults with prediabetes and hypomagnesaemia.

Guerrero-Romero, F et al. Oral Magnesium supplementation improves insulin sensitivity in non-diabetic subjects with insulin resistance. A double-blind placebo-controlled randomized trial, Diabetes & Metabolism. 2004; Volume 30, Issue 3, 253–258.

Kazaks AG, Uriu-Adams JY, Albertson TE, Shenoy S, Stern JS. Effect of Oral Magnesium Supplementation on Measures of Airway Resistance and Subjective Assessment of Asthma Control and Quality of Life in Men and Women with Mild to Moderate Asthma: A Randomized Placebo Controlled Trial, Journal of Asthma. 2010; Vol. 47, Iss. 1.

MICROBIOME

RANDOMISED CONTROLLED TRIALS

Ducrotté, P, Sawant, P, Jayanthi, V. Clinical trial: Lactobacillus plantarum 299v (DSM 9843) improves symptoms of irritable bowel syndrome. World Journal of Gastroenterology. 2012; 18(30), 4012–4018. http://doi.org/10.3748/wjg.v18.i30.4012.

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COENZYME Q10

RANDOMISED CONTROLLED TRIALS

Mortensen SA, Rosenfeldt F, Kumar A, Dolliner P, Filipiak KJ, Pella D, Alehagen U, Steurer G, Littarru GP. Q-SYMBIO Study Investigators. The effect of coenzyme Q10 on morbidity and mortality in chronic heart failure: results from Q-SYMBIO: a randomized double-blind trial. JACC. Heart failure. 2014; ISSN: 2213-1787, Vol: 2, Issue: 6, Page: 641-9.

Western Herbal Medicine

OVERVIEW

A 2005 Cochrane review of 37 double blind randomised studies of Hypericum (St John's Wort) showed an improvement in symptoms of mild to moderate

depression, more than a placebo did, with benefits similar to the results of conventional drug therapy.

A 2008 Cochrane systematic review highlighted similar benefits with Hypericum in major depression and noted fewer side effects than conventional anti-depressants.

Ebrahimzadeh Attari, V., Malek Mahdavi, A., Javadivala, Z., Mahluji, S., Zununi Vahed, S., & Ostadrahimi, A. (2018). Review of A systematic review of the anti-obesity and weight lowering effect of ginger (Zingiber officinale Roscoe) and its mechanisms of action. Phytotherapy research : PTR, 32(4), 577–585. https://doi.org/10.1002/ptr.5986

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Ghazanfarpour, M. *et al.* (2016) 'The efficacy of Iranian herbal medicines in alleviating hot flashes: A systematic review', *International Journal Of Reproductive Biomedicine (Yazd, Iran)*, 14(3), pp. 155–166. http://search.ebscohost.com/login.aspx?direct=true&db=mdc&AN=27294213&site=ehost-live

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Shiatsu

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