AHC Media

Integrative Medicine

Vol. 17, Issue 9, September 2014
www.ahcmedia.com

Evidence-based summaries and critical reviews on the latest developments in integrative therapies [ALERT]

DIETARY SUPPLEMENTS

ABSTRACT & COMMENTARY

Dietary Supplements and Prescription Drugs: Concomitant Use Continues to Rise

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Dr. Sasser reports no financial relationships relevant to this field of study.

SYNOPSIS: Two recent studies have found that concomitant use of prescription medications and dietary supplements is common. Factors associated with concomitant use include female sex and older age. These findings reinforce the need for frequent communication between physicians and their patients about the full treatment "portfolio" to avoid undesirable interactions.

SOURCES: Farina EK, et al. Concomitant dietary supplement and prescription medication use is prevalent among U.S. adults with doctor-informed medical conditions. *J Acad Nutr Diet* 2014 Apr 4; pii: S2212-2672(14)00106-3. doi: 10.1016/j.jand.2014.01.016. [Epub ahead of print].

Kiefer DS, et al. The overlap of dietary supplement and pharmaceutical use in the MIDUS national study. *Evid Based Complement Alt Med* 2014;2014:823853. doi: 10.1155/2014/823853. Epub 2014 Apr 16.

The use of prescription medications (PM) is ubiquitous among Americans. A 2013 study found that 68% of those surveyed took at least one PM regularly and slightly more than half took two or more.[1] Other studies have found that as many as 50% of Americans use one or more dietary supplements (DS) regularly.[2] The potential for PM-DS interactions (as well as PM-PM and DS-DS effects) is a pressing medical concern and the subject of continuing population research. In the first half of 2014, two groups published findings on the frequency and

Financial Disclosure: *Integrative Medicine Alert*'s executive editor David Kiefer, MD, peer reviewer J. Adam Rindfleisch, MD, MPhil, AHC Media executive editor Leslie Coplin, and managing editor Neill Kimball report no financial relationships relevant to this field of study.

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Integrative Medicine [ALERT]

Integrative Medicine Alert,
Integrative Medicine Alert (ISSN 1096-942X) is published monthly by AHC Media LLC, One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850, Atlanta, GA 30326.

Periodicals Postage Paid at Atlanta, GA, and at additional mailing offices.

GST Registration Number: R128870672.
POSTMASTER: Send address changes to *Integrative Medicine Alert*, P.O. Box 550669, Atlanta, GA 30355.

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characteristics of concomitant PM and DS use. This article summarizes both papers and considers the impact of their findings.

Farina and colleagues extracted PM and DS data from the 2005-2008 cycle of the National Health and Nutrition Examination Survey (NHANES). The NHANES subset used for study (n = 9950) was weighted to represent the U.S. population > 20 years of age. Aside from those with missing data, the only significant exclusion was pregnancy. Use of PM and DS (both in the past 30 days) was recorded through participant interviews with computer-based aids to guide accurate, standardized classification. Participants also reported on a number of "doctor-informed medical conditions" (DIMC) (i.e., "Has a doctor ever told you that you have…"), grouped in broad categories such as cancer, heart/vascular, and respiratory.

Of the NHANES sample, 57.1% of respondents reported using at least one PM, 51.3% reported using at least one DS, and 34.3% reported using both. Those with any DIMC were more than twice as likely to report concomitant PM and DS use than those with none (odds ratio [OR], 2.62; 95% confidence interval [CI], 2.13-3.21). Others more likely to report concomitant use were women, those with more education (a gradient from less than high school to college graduate), and older people (60 years or older, as compared with those age 20-39 and age 40-59). Study respondents using more than one PM or DS were also significantly more likely to report use in both categories (OR, 1.41; 95% CI, 1.20-1.66; and OR, 1.57; 95% CI, 1.26-1.97, respectively).

Kiefer and colleagues analyzed data from Phase 2 of the Midlife in the United States (MIDUS 2) study. MIDUS was a national survey conducted using random-digit dialing and other techniques. Participants were residents of the continental United States between the ages of 25 and 74 years. Those completing a telephone survey and a self-report questionnaire (n = 3876) were included in the present analysis. The questionnaire included items in which respondents identified medical conditions for which they had taken PM, and identified DS they used, in both cases from choices on a list and in the past 30 days.

Of the MIDUS population, 67.6% reported using at least one PM, 69.7% reported using at least one DS, and 49.6% reported using both. Those reporting use of both PM and DS were more likely to be female, were older on average, less affluent (based on median income), and somewhat less well educated as compared with those reporting no use in either category. Those reporting PM and DS use were also more likely to be female and older, as compared with those reporting PM use only.

■ COMMENTARY

These reports are a striking indication of the extent to which a variety of substances have become a routine part of many Americans' health care practices. It would appear that DS are part of both the preventive care routine and the response to disease, although it is not possible to tell from these data whether either kind of use originates in patient desires, practitioner recommendations, or a combination of both. Also striking are the indications that concomitant use cuts across some demographic categories. Although it is clear that PM+DS users are more likely to be female, the NHANES population showed greater use among those with more education, while the MIDUS population showed higher use among those with less education. Similarly, MIDUS concomitant users were more likely to be less affluent, while the NHANES study showed a more even distribution across levels of income. In this context, it is worth repeating that both studies included nationwide (in the case of MIDUS continental United States) samples. These results go beyond the usual hotbeds of complementary and alternative medicine use.

Even as use of DS appears to be spreading, it is important to be clear

Summary Points

- Two recent reports of population surveys show rates of dietary supplement use between 50% and 70%.
- One report shows those who have clinically confirmed medical conditions are more than twice as likely as those without such conditions to report using both prescription medications and dietary supplements.
- Women and the elderly are also more likely to combine prescribed drugs and dietary supplements.

about what exactly counts as DS. The NHANES study used 18 categories that included, among other things, multivitamins, multiminerals, amino acids, botanicals, calcium, probiotics, and antacids in over-the-counter (OTC) formulations. It also was careful to note when PM were formulated to include ingredients that would otherwise be considered DS (for instance, a statin with niacin), and when substances could be either OTC or by prescription, depending on dose. The MIDUS study asked about vitamin, mineral, or herbal supplements. The breadth of what might count as DS use, and the possibility of "double-dipping" — the same agent being taken in OTC and prescription forms — complicates the clinician's task in sorting out with the patient what he or she is taking and with what therapeutic goal.

And yet, the message clearly is that this kind of inventory is more and more urgent. Stories of elderly patients coming to doctors' visits with shopping bags of prescription medications might pale in comparison with stories of such patients coming in with both their prescription medications *and* their supplements. The lists may be long, but the need is great. Several popular DS are known to have significant interactions with PM. St. John's wort, ginseng, and gingko are among the DS best studied in this respect, but others likely have the potential to alter, up- or down-regulate the effects of various PM.[3] This, of course, is in addition to the many known and suspected interactions among PM, and between PM and foods not generally thought of as DS (for instance, grapefruit and its effect on the cytochrome P450 drug metabolism pathway).[4]

Editor's Note: Some clinicians also use the H.E.R.B.A.L. mnemonic to guide their exploration and instruction of patients' dietary supplement use.

H: Hear the patient out
E: Educate the patient about sources of information and products
R: Record in the chart
B: Be aware of adverse effects and interactions
A: Agree to discuss
L: Learn and keep learning

Adapted from: Bonakdar RA, ed. *The H.E.R.B.A.L. Guide: Dietary Supplement Resources for the Clinician*. Philadelphia; Lippincott Williams & Wilkins; 2010.

With these considerations in mind, it is possible to make a few recommendations for clinicians who need to review the totality of PM and DS use with their patients:

1. **Don't wait to be asked.** The data make clear that more people than not are using DS — defined broadly — at least some of the time. Asking a patient about his/her DS use opens the door to conversation and may ease any concerns patients may have about admitting to using "unofficial" remedies.

2. **Be systematic.** The Farina article includes an appendix listing the 18 categories of DS included in the NHANES survey. A paper or electronic version of such a list could be a good tool to use during a clinical interview.

3. **Ask clarifying questions.** If a patient says that s/he uses some substance, appropriate questions about dose, delivery form/format, frequency, and therapeutic purpose(s) should follow. Bear in mind that some DS have multiple uses (for example, antacids used for their labeled indication and/or as sources of calcium or other minerals). Note also that some supplements contain multiple agents.

4. **Ask often.** Patients' DS portfolios can be expected to change and will need periodic updating. DS use is pragmatic and driven by many factors including cost, availability, assessment of effects, and even seasonal variation (for example, Vitamin D supplementation in northern latitudes in the winter months). Here again, asking about therapeutic goals may help to guide a discussion of various brands and formulations and reveal important details about patterns of DS use.

5. **Be respectful.** Patients can recognize when a clinician is skeptical or dismissive. This may inhibit current and future discussions. It is never wrong to point out potentially problematic side effects or interactions, but doing so in a way that shows respect for the patient's autonomy and capacity to make informed choices increases the chance that such messages will be given due consideration. ■

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OSTEOPATHIC MANIPULATIVE THERAPY

ABSTRACT & COMMENTARY

Osteopathic Manipulation in Pregnancy: Benefits for Low Back Pain

By David Kiefer, MD

SOURCE: Hensel KL, et al. Pregnancy Research on Osteopathic Manipulation Optimizing Treatment Effects: The PROMOTE study a randomized controlled trial. *Am J Obstet Gynecol* 2014 Jul 25. pii: S0002-9378(14)00792-3. doi: 10.1016/j.ajog.2014.07.043 [Epub ahead of print].

This research study, called PROMOTE (Pregnancy Research in Osteopathic Manipulation Optimizing Treatment Effects), randomized 400 women in their third trimester to usual obstetrical care (n = 133), usual care plus osteopathic manipulative therapy (OMT) (n = 136), or usual care plus a placebo ultrasound treatment (n = 131). The OMT and placebo ultrasound treatments involved seven approximately 20-minute treatments over 9 weeks, both over the same body regions, areas such as the thoracic and lumbosacral paraspinal musculature, hip, and anterior pelvis. The primary outcomes were self-assessments for pain and back-related outcomes. In addition, medical records were reviewed for delivery outcomes, most notably the presence of meconium-stained amniotic fluid, a decrease that is postulated to represent less maternal stress from pain and less fetal stress. The back pain and functioning scales used were the Quadruple Visual Analog Scale, Characteristic Pain Intensity, and the Roland-Morris Low Back Pain and Disability Questionnaire.

Women aged 18-35 with an estimated gestational age of at least 30 weeks were recruited for this study from three OB-Gyn clinics in Texas. Exclusion criteria included the presence of any high-risk conditions (such as gestational diabetes, pre-eclampsia/eclampsia, oligohydramnios, or vaginal bleeding) or the use of any other body-based therapies such as massage, chiropractic, physical therapy, or additional OMT.

Only 99 women completed all seven treatment visits and were analyzed according to an intention-to-treat analysis. According to this analysis, OMT significantly moderated the progression of back pain and deterioration of functioning ($P < 0.001$ for both); alternatively stated, the usual care group showed a worsening of pain and functioning as time progressed. The OMT effects, interestingly, were comparable to the placebo ultrasound group. A per-protocol analysis was done for women who completed at least four of the seven visits (n = 357), in order to use the data collected on women who delivered before term. These results agreed with the intention-to-treat analysis for the 99 women as previously described.

Meconium staining information was available on 329 women; a logistic regression indicated that there was no difference between the three groups with respect to risk of meconium staining. One interpretation of this offered by the authors is that OMT causes no additional risk in women in their third trimester.

Summary Points

- Osteopathic manipulative therapy (OMT) during the third trimester appears to help prevent the progression of back pain and the loss of back functioning with time.
- OMT and a placebo ultrasound treatment have comparable effects on back pain and functioning.

■ COMMENTARY

The authors of this study make a compelling case for their investigations, namely that 70%

of women have back pain during pregnancy, and many of the options available (i.e., pharmaceuticals) may not be safe for the woman or fetus. One class of integrative therapy, manipulative body-based approaches, avoids the concerns about ingested substances during pregnancy, and includes several techniques, including OMT. The authors define OMT as "the therapeutic application of manually guided forces by an osteopathic physician to improve physiologic function and/or support homeostasis that has been altered by somatic dysfunction." They further quote studies that pin part of the mechanisms of action of OMT on "increasing range of motion, improving tissue texture, and decreasing pain."

With this as a background, these results show that OMT during the third trimester appears to help prevent the progression of back pain and the loss of back functioning with time. And, if meconium staining of amniotic fluid as an indirect measurement of safety is believed, OMT appears not to be harmful for women or fetuses. An equally important component of the results of this study is the fact that the OMT group and the placebo ultrasound group had a similar attenuation of the progression of back pain and loss of back functioning. The authors ascribe this to the known benefits of "time, touch, intention, and interaction" present in both groups. Such an effect, surely, is consistent with many clinicians' sense as well as with other studies on the increased benefits beyond pharmaceutical treatments that manipulative therapies provide for pain.[1]

Should all women in their third trimester receive OMT? The equivalence with the placebo ultrasound therapy speaks pretty strongly in favor of all women in their third trimester receiving *some* body-based therapy. This study didn't analyze the effect of massage or chiropractic (in the exclusion criteria), but a reasonable extrapolation would include such treatments as ones that might help women progress less in back pain and loss of functioning. Cost and inconvenience might be the only two reasons not to suggest this avenue of treatment and prevention for women heading into their third trimester. Another compelling aspect to this work is the fact that this demographic has limited options for the treatment of pain; it is nice to be able to offer something. ■

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GENETIC TESTING

MTHFR Clinical Considerations: A Review

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Dr. Pantuso reports no financial relationships relevant to this field of study.

The methylenetetrahydrofolate reductase (MTHFR) enzyme is centrally involved with both folate and homocysteine metabolism (*see Figure 1*). The MTHFR enzyme irreversibly converts 5,10 methylenetetrahydrofolate to 5-methyltetrahydrofolate, which is the primary circulatory form of folate. 5-methyltetrahydrofolate is also a cosubstrate in the remethylation of homocysteine to produce methionine.[1-3] Methionine is the precursor to S-Adenosyl methionine (SAMe) and is one of the essential amino acids in that it is required through dietary intake.[1-3] SAMe is a major methyl donor and is involved in numerous biological reactions including the epigenetic mechanism of DNA methylation.[2]

Polymorphisms of the MTHFR gene are a major cause of hyperhomocystinemia of unknown clinical significance.[3,4] At first, elevated homocysteine levels were thought to be a major risk factor for cardiovascular disease (CVD),[3-5] but this has softened lately. Recent research has demonstrated that moderately elevated homocysteine levels are weakly correlated with coronary heart disease risk. A recently published meta-analysis that investigated unpublished data sets demonstrated that moderately elevated homocysteine levels do not affect coronary heart disease risk.[6]

MTHFR gene polymorphisms also have been associated with a long list of disease conditions

Summary Points

- C677T and A1298C polymorphisms are common variants in the MTHFR gene.
- At this point, only C677T homozygous variant with elevated plasma homocysteine level is clinically significant.
- Patients with a C677T homozygous without elevated plasma homocysteine level do not have an increased risk of venous thromboembolism or recurrent pregnancy loss related to their MTHFR status.
- Patients with a C677T homozygous variant with elevated plasma homocoysteine level do have a slightly increased risk of venous thromboembolism, and recurrent pregnancy loss.

including autism, cancer, hypertension, aneurysm, recurrent pregnancy loss, peripheral artery disease, migraine, and neuropsychiatric disease.[1-3,5]

Most of the association data with MTHFR are contradictory and there is no clear evidence to suggest a causal relationship.[1,5,7] Nonetheless, MTHFR gene testing has become exponentially more popular in the last few years.

With the introduction of genetic testing that is increasingly affordable, more patients are approaching their health care providers about such testing or with results from their direct-to-consumer genetic tests. Research findings linking MTHFR gene polymorphisms and disease risk have been conflicting. This has led to challenges as far as interpreting such data.[7]

This review article will provide the following:

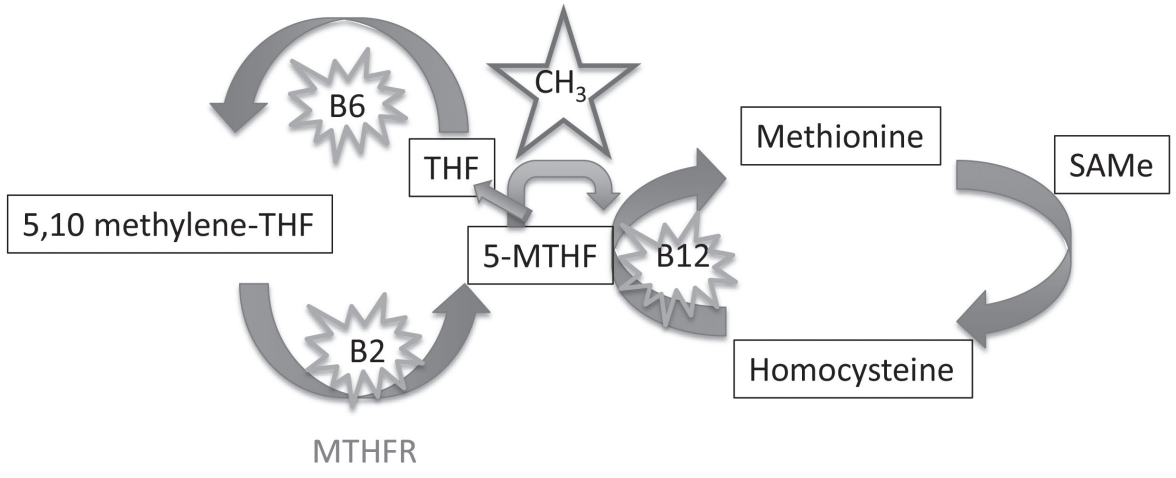
- Background on the MTHFR gene and its known functions
- MTHFR polymorphisms and mutations and their association to diseases
- Bottom line recommendations on ordering MTHFR genetic testing.

BACKGROUND

The MTHFR gene is located on chromosome 1 and expression of the MTHFR enzyme has been found in most body tissues.[3] In 1972, Mudd et al found that a patient with homocystinuria had a rare and severe deficiency in the MTHFR enzyme.[8] In 1988, the thermolabile variant of MTHFR enzyme was isolated from lymphocytes in patients with CVD who also had a mild-to-moderate increase in homocysteine, which at the time was an emerging risk factor for CVD.[9] Frosst et al first demonstrated the association between homozygous C677T genotype and mild hyperhomocysteinenia in the NHLBI Heart Study.[7] This correlation between the C677T homozygous variant and elevated homocysteine was found only to occur in the presence of low folate status.[7]

Figure 1. Schematic Representation of Homocysteine and Folate Metabolism

The MTHFR (methylenetetrahydrofolate reductase) enzyme converts 5,10 methylenetetrahydrofolate (5,10 methylene-THF) into 5-methyltetrahydrofolate (5-MTHF), which requires B2 (riboflavin) as a cofactor. 5-MTHF donates a methyl group in the reaction converting homocysteine to methionine, which requires B12 as a cofactor. B6 (pyridoxine) is required in the conversion of tetrahydrofolate (THF).



MTHFR POLYMORPHISMS

According to the National Center for Biotechnology Information of the National Institutes of Health, there are nine common polymorphic variants of MTHFR, and 34 rare and deleterious mutations are documented.[3] The clinical presentation of MTHFR deficiency resulting from these mutations is highly variable and may include everything from neurological deterioration and death in infancy to mild thrombophilia in adults.[10-12]

The two most common polymorphic variants that affect enzyme activity are the C677T and the A1298C variants.[3] The C677T and the A1298C variants are the polymorphisms that are analyzed through most laboratory MTHFR genetic tests in the United States.[5,7] The 34 rare and deleterious mutations require gene sequencing, which is not widely available.

Because there are two copies of each gene, an individual can be homozygous for the C677T variant. This can cause hyperhomocysteinemia if the individual also has a low plasma folate.[3-6] Individuals who are heterozygous for C677T have one copy of the C677T variant and one "wild type" or normal copy. These C677T heterozygous individuals do not demonstrate elevated homocysteine. C677T homozygous variant enzyme is thermolabile and demonstrates 70% reduced enzyme activity in vitro.[3] The heterozygous C677T MTHFR enzyme has 35% reduced activity in vitro.[3] It is estimated that 32% of Mexicans, 10-15% of North American Caucasians, and 6% of people of African descent are C677T homozygous.[3]

Another common variant is the A1298C polymorphism. Neither A1298C homozygosity nor heterozygosity causes elevated homocysteine levels.[3,5] The A1298C variant has demonstrated decreased enzyme activity in vitro; however, it has not demonstrated thermolability. C677T is inherited in an autosomal recessive pattern.[5] The C677T and A1298C variants are in linkage disequilibrium with each other, making compound heterozygosity an infrequent occurrence.[13]

DISEASE CONNECTIONS

There have been numerous, often contradictory, studies investigating the role of MTHFR variant genotype status, but different medical conditions with no clear positive relationship has been demonstrated.[1,3,5]

In a recent meta-analysis comparing unpublished data with published data investigating the role of MTHFR polymorphism and coronary heart disease, the authors found no relationship between MTHFR polymorphism status and risk of coronary heart disease.[6] A recent study reported that elevated plasma homocysteine did increase the risk of coronary heart disease. However, this was independent of the MTHFR genotype.[14]

Research has demonstrated that there is increased risk (odds ratio, 1.6) of a woman who is homozygous for the C677T variant having offspring with a neural tube defect.[5,15] The risk of neural tube defects are further increased if both the mother and the fetus are homozygous for the C677T variant.[5,15]

Another area of research that may demonstrate importance in the future is investigating the differential effects of certain pharmaceutical drugs on MTHFR genotype status.[3] Of particular interest in this field of research is whether there is a differential effect of anti-folate medications on individuals with MTHFR polymorphisms and mutations.[1,3,5]

EFFECT OF DIET ON MTHFR GENE EXPRESSION

Plasma homocysteine levels are dependent on nutritional, genetic, and environmental factors, and this may be mediated through MTHFR. In addition, the vitamins folate, B12, and B6 are required for homocysteine metabolism (*see Figure 1*). An Italian study investigating forms of folate (dietary, 5-MTHF, and folic acid) and effect on total plasma homocysteine levels found that all three experimental groups had lowered plasma homocysteine levels compared to the controls. Italy has not mandated folic acid food fortification, so the average folic acid intake through diet is 220 µg/day.[16] The study showed that a folic acid-enriched food diet (400 µg/day), supplemental folate in the form of 5-MTHF (200 µg/day), and folic acid (200 µg/day) are comparable in reducing total homocysteine levels irrespective of MTHFR genotype status.[16] Although supplementation of folic acid, B12, and B6 may lower plasma homocysteine, it does not appear that they affect CVD risk.[17]

Folic acid, also known as vitamin B9, is a synthetic vitamin that is not found in large amounts in food. Folic acid is stable while the natural forms of folate are unstable.[18-20] There are numerous forms of dietary folate. The folate that is most commonly found in foods is in the form of polyglutamates and must be converted into the monoglutamate form at the brush border

of the intestine to be absorbed. Folic acid is already in the monoglutamate form so it is easily absorbed. Folic acid must be converted into tetrahydrofolate (THF) by an enzyme named dihydrofolate reductase. THF then must undergo a number of steps to be finally converted into the active form of 5-MTHF by the enzyme MTHFR. 5-MTHF is the most common form found in the bloodstream.[18-20] Research is ongoing to determine whether supplementation of folic acid or 5-MTHF is preferred. Numerous enzymes and pathways are involved in folate absorption, metabolism, and trafficking throughout the body. The best form of supplemental folate is unresolved; folic acid or 5-MTHF appear to both be good choices.[17] More research is needed to understand any differences in absorption, metabolism, and trafficking of folic acid vs 5-MTHF.

RIBOFLAVIN

The MTHFR enzyme requires the cofactor flavin adenine dinucleotide (FAD). FAD has been shown to stabilize the MTHFR enzyme in vitro.[3,21] As riboflavin is the precursor to FAD, a diet rich in riboflavin may help to stabilize the MTHFR enzyme.

BETAINE/CHOLINE

Betaine and choline also act as methyl donors to convert homocysteine to methionine and have demonstrated total plasma homocysteine lowering effects in humans.[19] Betaine supplementation has been shown to lower homocysteine levels in both healthy subjects and patients with severe decreased MTHFR activity.[22-23]

SUMMARY

The MTHFR gene is complex and how it influences health requires much more research to fully understand the functions of the gene and how it is regulated. There is an MTHFR mouse model that may also help to shed light on the role of the MTHFR genotypes and their functions in other diseases.[3]

TESTING

Most experts recommend to not test for MTHFR polymorphisms C677T and A1298C in the general population. The American College of Medical Genetics (ACMG) does *not* recommend that MTHFR polymorphism testing be performed for the evaluation of thrombophilia or recurrent pregnancy loss. ACMG also recommends that clinicians do *not* order testing for at-risk family members. The ACMG recommends that women of childbearing age take daily folic acid according to the general population guidelines to prevent neural tube defects regardless of MTHFR status.

None of the following medical associations recommend ordering C677T polymorphism testing with or without elevated homocysteine in persons with inherited thrombophilia or thrombosis:

- American College of Medical Genetics
- American College of Obstetrics and Gynecology
- College of American Pathologists
- American College of Chest Surgeons
- British Hematology Standards Committee

Only the American Heart Association states that it is optional whether to order a C677T polymorphism test if elevated homocysteine is present.[7]

Despite the recommendations of numerous medical associations, MTHFR testing is one of the most commonly ordered molecular pathology tests in the United States.[7] In one study, only 14.5% of MTHFR gene polymorphism testing was conducted after a total plasma homocysteine test was found elevated and for thrombophilia or thrombosis.[7] Sixty-four laboratories in North America, along with a number of direct-to-consumer laboratories, offer the MTHFR testing.[3,7]

According to ACMG practice guidelines, "it is not uncommon that medical problems are incorrectly attributed to positive MTHFR status and that the geneticist should ensure that patients have received thorough and appropriate evaluations for their symptoms."[5]

Total plasma homocysteine can be ordered and if it is elevated, dietary interventions should be initiated. It is important to note that total homocysteine levels increase with age and are lower in pregnant populations. Total homocysteine levels are also influenced by ethnicity to an unknown degree, so caution is warranted when interpreting results.

Some clinicians only use such predictive genetic tests when the result will significantly influence the clinical management of a patient. An example of this is ordering a genetic test because a treatment is available for the medical condition or disease caused by the mutation. It can be difficult to predict the many downstream effects of some genetic tests, MTHFR included, making a strong case to involve genetic counselors or clinicians with specialized training when determining the appropriateness of gene analysis in a given patient circumstance.

Table 1. RDA/Adequate Intakes for Folate, Riboflavin, Pyridoxine, Cobalmin, and Choline

Nutrient	RDA for Adult Males	RDA for Adult Females	RDA for Pregnant Females
Folate	400 µg/day	400 µg/day	600 µg/day
Riboflavin (B2)	1.3 mg/day	1.1 mg/day	Not specified
Pyridoxine (B6)	19-50 years old = 1.3 mg/day > 50 = 1.7 mg/day	19-50 years old = 1.3 mg/day > 50 = 1.5 mg/day	Not specified
Cobalmin (B12)	2.4 µg/day	2.4 µg/day	Not specified
Choline (adequate intake)	550 mg/day	425 mg/day	Not specified

Adapted from: Dietary Reference Intakes for Calcium, Phosphorous, Magnesium, Vitamin D, and Fluoride (1997); Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline (1998); Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids (2000); and Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc (2001); Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate (2005); and Dietary Reference Intakes for Calcium and Vitamin D (2011). These reports may be accessed via www.nap.edu.

RECOMMENDATION

According to research and the numerous medical organizations, there is insufficient evidence to support testing for the MTHFR polymorphisms C677T and A1298C in most cases. However, if a clinician suspects that one of these genetic tests is warranted, a referral to a genetic counselor could be considered. One of the reasons for such a referral is that the MTHFR polymorphism testing for C677T and A1298C does not rule out rare and severe mutations of the gene, and gene sequencing would then be required. Also, unnecessary testing can carry risks. For example, patients receiving a homozygous C677T or A1298C result may experience psychological stress, even though the overwhelming body of evidence is inconclusive.[5]

A healthy diet containing folate, choline, betaine, riboflavin, B6, and B12 should be recommended for everyone, especially individuals who have MTHFR polymorphisms (*see Table 1*). One of the reasons for this, as described above, is that the C677T homozygous polymorphism combined with low dietary folate leads to elevated homocysteine, a situation that can be reversed with a change in diet. Folate-rich foods include dark green leafy vegetables and legumes. Choline-rich foods include high-quality organic/grass fed red meat, poultry, eggs, and fish. Betaine-rich foods include wheat bran, wheat germ, beets, and riboflavin-containing foods (mushrooms and almonds). B6 sources include fish, poultry, nuts and legumes, and B12 sources are high-quality organic/grass-fed red meat, poultry, and fish.

The decision of whether to supplement with folate, choline, betaine, riboflavin, B6, and B12 in people with MTHFR mutations is more complicated; there are no data suggesting that supplementation improves disease outcomes. ■

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PROBIOTICS

SHORT REPORT

Probiotic Supplementation Reduces Upper Respiratory Tract Infections

By Donald Brown, ND

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Dr. Brown reports he is a retained consultant for Nature's Way and Linnea.

SOURCE: West NP, et al. Probiotic supplementation for respiratory and gastrointestinal illness symptoms in healthy physical active adults. *Clin Nutr* 2014;33:581-587.

This 150-day, randomized, double-blind, placebo controlled trial (RCT) with 465 healthy adult volunteers (mean age 37 years old) was designed to examine the effects of probiotics on the incidence of upper respiratory tract infections (URTI). Participants were assigned to one of three groups:

1. *Bifidobacterium animalis* subsp. *lactis* Bl-04 (2×10^9 cfu/day);
2. *Lactobacillus acidophilus* NCFM and *Bifidobacterium animalis* subsp. *lactis* Bi-07 (5×10^9 cfu of each strain per day); or
3. Placebo.

Each preparation was delivered in a powder to be mixed into a cold beverage. At the end of the study, participants taking the Bl-04 had an approximate 27% reduction in risk of UTRI compared to the placebo group ($P = 0.022$). There was no significant difference in the number of UTRIs between the NCFM/Bi-07 group and the placebo group ($P = 0.15$). Both probiotic supplement regimens were associated with a delay in time to a UTRI of approximately 0.8 months compared to placebo.

The results of this trial continue to support the use of probiotics for the prevention of UTRIs. They add to the positive findings of a 2011 Cochrane Review meta-analysis of 10 RCTs which concluded that probiotics were superior to placebo in reducing the incidence of acute UTRIs in adults and children as well as reducing antibiotic use.[1] It's interesting to note that a similar trial with preschool age children (included in the meta-analysis above) found that the combination of *L. acidophilus* NCFM and Bi-07 was effective in reducing the incidence of UTRIs.[2] It is hard to speculate why the combination was not as effective with adults. ■

Summary Points

- Daily intake of a single strain probiotic supplement (Bl-04) was associated with a decreased risk of UTRIs in healthy adults.
- The results continue to support the use of probiotics as a tool for the prevention of UTRIs in adults as well as children.

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SHORT REPORT

Can Probiotics Affect Blood Pressure?

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SOURCE: Khalesi S, et al. Effect of probiotics on blood pressure: A systematic review and meta-analysis of randomized, controlled trials. *Hypertension* 2014; doi: 10.1161/HYPERTENSIONAHA.114.03469.

A meta-analysis of nine clinical trials was completed to determine the effect of probiotics on blood pressure (BP). The total number of participants was 543 and the included studies were all parallel, randomized, controlled trials, with seven studies reporting a double-blind design. Of the nine studies, three included healthy participants, two included patients with hypercholesterolemia, one included patients with hypertension, one included overweight and obese subjects, and one included patients with metabolic syndrome. Four studies used yogurt as the source of probiotic bacteria, two used fermented and sour milk, one study used encapsulated probiotics, one used a probiotic rose-hip drink, and another used probiotic cheese. Four studies used a single strain of the probiotics, while four used two strains and one used a combination of three strains. The daily dose of probiotics ranged from 10^9 colony forming units (cfu) to 10^{12} cfu and the duration ranged from 3 weeks to 9 weeks.

Eight of the studies reported a reduction in systolic blood pressure (SBP) with a mean reduction ranging from 1.07 to 14.10 mmHg. Five studies reported a clinically significant reduction in SBP of > 5 mmHg. When all nine studies were considered, there was a significant reduction of SBP by 3.56 mmHg (95% confidence interval [CI], -6.46 to -0.66; $P < 0.001$) compared with control groups. Eight of the studies reported changes in diastolic blood pressure (DBP) but only two reached a statistically significant level. The meta-analysis found a significant reduction of 2.38 mmHg (95% CI, -3.84 to -0.93; $P < 0.01$). A greater reduction for both SBP and DBP was found in studies using multiple strains as opposed to only one. Participants with BP > 130/85 were more likely to show significant improvement compared to those with BP < 130/85. Better results were also observed in studies > 8 weeks in duration and also those studies that used probiotic potencies of ≥ 10^{11} cfu per day. ■

Summary Point

- Consuming probiotics may have a modest effect on blood pressure (BP), especially in persons with BP > 130/85 mmHG and when taken for ≥ 8 weeks as multistrain product at a potency of ≥ 10^{11} colony forming units per day.

CME INSTRUCTIONS

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CME QUESTIONS

1. According to the NHANES and MIDUS surveys, those reporting use of both prescription drugs and dietary supplements are more likely to be:
a. between 20 and 45 years of age.
b. between 40 and 60 years of age.
c. over age 60.

2. Which of the following is true regarding the use of osteopathic manipulative therapy (OMT) during the third trimester of pregnancy as found by Hensel et al?
a. OMT is more effective in alleviating back pain than placebo ultrasound treatments.
b. Compared to the control group, OMT prevented the worsening of back pain and as well as the deterioration of back functioning during the third trimester.
c. OMT caused more meconium staining of amniotic fluid than the control group or the ultrasound group.
d. There are minimal applications of these research results given the rarity of back issues during pregnancy.

3. Which of the following interventions with folate decreased total plasma homocysteine levels in an Italian population that has a 220 µg/day dietary contribution irrespective of MTHFR polymorphism status?
a. 1200 µg/day of 5-MTHF
b. 800 µg/day of folic acid supplementation
c. 200 µg/day of additional folate rich foods
d. 5 mg/day of 5-MTHF

4. Which individual with a MTHFR genetic variant is at increased cardiovascular risk?
a. Homozygous C677T variant with increased plasma homocysteine level
b. Heterozygous C677T variant with normal plasma homocysteine levels
c. Heterozygous C677T with normal plasma homocysteine levels
d. Compound heterozygous C677T and A1298C variants

5. A meta-analysis suggests that consumption of probiotics may modestly reduce blood pressure. What factors are most likely to improve this outcome?
a. Consuming probiotics in potencies ≥ 10^{11} colony forming units per day
b. A baseline BP of ≥ 130/85 mmHG
c. Taking a multi-strain probiotic supplements
d. All of the above

6. A recent study found that daily intake of a probiotic supplement in healthy adults was associated with decreased risk of:
a. irritable bowel syndrome.
b. upper respiratory tract infections.
c. insomnia.
d. All of the above

[IN FUTURE ISSUES]

Vitamin D: Review of recent meta-analyses

MDMA for post-traumatic stress disorder

Energy medicine concepts and interventions