AHC Media

Integrative Medicine

Vol. 20, Issue 1, January 2017
AHCMedia.com

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

STRESS

ABSTRACT & COMMENTARY

The Effect of Stress on Food

By William C. Haas III, MD, MBA

Assistant Professor, Department of Family and Community Medicine, Arizona Center for Integrative Medicine, University of Arizona, Tucson, AZ

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

SYNOPSIS: Stress experienced prior to eating may raise inflammation levels as much as eating a high saturated fat meal in a relaxed state.

SOURCE: Kiecolt-Glaser JK, Fagundes CP, Andridge R, et al. Depression, daily stressors and inflammatory responses to high-fat meals: When stress overrides healthier food choices. *Mol Psychiatry* 2016; Sept 20. Doi: 10.1038/mp.2016.149 [Epub ahead of print].

The role of inflammation in the development of chronic disease has garnered significant attention among researchers and clinicians. Likewise, the contribution of dietary intake to the inflammatory response has driven new lines of nutritional research and the recent development of "anti-inflammatory" diets. Extensive research supports the benefit of Mediterranean-based anti-inflammatory diets, especially as it relates to reduced inflammation and improved disease outcomes.[1,2] However, other lifestyle factors beyond diet contribute to inflammation within the body. Stress and depressed mood both have been linked with increased inflammation.[3] When considering diet and mood together, an interesting question arises — does stress affect the inflammatory response of food?

A group of researchers who followed healthy breast cancer survivors attempted to assess the effect of stress as well as depressed mood on the metabolic response to two different high-fat meals. The primary hypothesis maintained that stressors occurring prior to a meal would raise postprandial inflammatory markers. Implied, yet equally important, was the hypothesis that a high saturated fat meal would increase inflammatory markers to a greater extent than a high oleic sunflower oil meal.

Financial Disclosure: *Integrative Medicine Alert*'s executive editor David Kiefer, MD, peer reviewer Suhani Bora, MD, AHC Media executive editor Leslie Coplin, and assistant editor Jonathan Springston report no financial relationships relevant to this field of study.

[INSIDE]

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.

SUBSCRIBER INFORMATION
(800) 688-2421
Customer.Service@AHCMedia.com
AHCMedia.com

Questions & Comments:
Please contact Executive Editor Leslie Coplin, at lcoplin@reliaslearning.com

Subscription Prices
United States
Print: 1 year with free *AMA PRA Category 1 Credits*™: $319
Add $19.99 for shipping & handling.
Online only: 1 year (Single user) with ***free*** *AMA PRA Category 1 Credits*™: $269

Multiple Copies: Discounts are available for group subscriptions, multiple copies, site-licenses, or electronic distribution.
For pricing information, please contact our Group Account Managers at Groups@AHCMedia.com or (866) 213-0844.

Back issues: $42. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Canada: Add 7% GST and $30 shipping.
Elsewhere: Add $30 shipping.

ACCREDITATION
AHC Media is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media designates this enduring material for a maximum of ***36*** *AMA PRA Category 1 Credits*™. Each issue has been designated for a maximum of 3.0 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

The American Osteopathic Association has approved this continuing education activity for up to 24 AOA Category 2-B credits.

This CME activity is intended for physicians and researchers interested in integrative medicine. It is in effect for 36 months from the date of the publication.

AHC Media

Summary Points

- Meals high in saturated fat increase postprandial inflammatory markers to a greater extent than meals high in monounsaturated fats.
- Recent stressors significantly increased the postprandial inflammatory response to a high-fat meal composed predominately of monounsaturated fats.
- Recent stressors did not affect the postprandial inflammatory response to a high-fat meal composed predominately of saturated fats.

Following a double-blind, randomized, crossover study, researchers assigned 38 breast cancer survivors and 20 healthy patients to receive one high saturated fat meal and one high oleic sunflower oil meal at two separate times (approximately 1-4 weeks apart). Patients were excluded from participating if they had a history of cardiopulmonary disease, autoimmune disease, diabetes, or cancer aside from breast cancer. Medications leading to exclusion included lipid-lowering drugs, antihypertensives, and/or any medications with immunological or endocrinological effects.

Both meals incorporated eggs, turkey sausage, and biscuits with gravy for a total of 930 kcal, consisting of 60% fat, 25% carbohydrate, and 15% protein. The fat content for each of the meals varied. The breakdown for the high saturated fat meal was 16.84 grams palmitic acid and 13.5 grams oleic acid (ratio 1.93), while the breakdown for the low saturated fat meal was 8.64 grams palmitic acid and 31.21 grams oleic acid (ratio 0.67). In an effort to standardize the effect of the test meals, participants were instructed to avoid alcohol one day prior to the study and strenuous physical activity two days prior. Additionally, participants were instructed to avoid all perceived anti-inflammatory medications and/or supplements one week prior to the interventions. Before each meal, participants also recorded the number of daily stressors over the previous 24 hours using the Daily Inventory of Stressful Events tool. Depression history was evaluated using DSM-IV criteria, and the Center for Epidemiological Studies Depression Scale assessed depressive symptomatology over the week prior to the interventions.

To evaluate the primary outcome of inflammation, blood samples were drawn before the meals and at 2, 4, and 7 hours after the meals. Samples were analyzed for levels of C-reactive protein (CRP), serum amyloid A (SAA), intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1), the latter two representing adhesion molecules known to reflect generalized inflammation and atherosclerotic plaque burden, respectively.[4]

At baseline, there were no significant differences among the biometric measurements between the control group and breast cancer survivors. The number of prior day stressors were equivalent between the two groups; however, breast cancer survivors were more likely to have a history of major depression. With regard to the primary variables, baseline fasting inflammatory makers were equivalent between the groups with the exception of ICAM-1, which was higher in breast cancer survivors. In the fasting state, there also were no associations noted between prior day stressors and inflammatory markers.

With regard to postprandial responses, the majority of the sampled inflammatory markers (CRP, ICAM-1, VCAM-1) were higher following the saturated fat meal compared to the high oleic sunflower oil meal when no stressors were reported (P = 0.04, 0.02, and 0.05, respectively). Interestingly, when accounting for prior day stressors, postprandial inflammatory markers rose significantly after the high oleic sunflower oil meal, but not after the high saturated fat meal. In fact, for each additional prior day stressor reported, CRP increased by 2.9% after the high oleic oil meal. There were no significant effects of depression history on inflammatory markers ($P > 0.07$ for all tests).

■ COMMENTARY

The effect of food and stress on inflammation has received significant attention because of their direct effects on health and well-being. The present study is one of the first to evaluate the ability of stress to modulate the inflammatory response of different food. Somewhat unexpectedly, the researchers found that prior stress exposure negated differences in inflammation resulting from a high saturated fat or a high oleic fat meal. In essence, consuming a meal with healthy fat while under stress resulted in the same amount of inflammation as an unhealthy fat-based meal. Equally intriguing was the finding that stress exposure did not further increase inflammation levels after consuming a saturated fatty meal. Unfortunately, the researchers were unable to account for why stress did not further increase inflammation levels after high saturated fat intake.

When interpreting the results of the study, some attention must be directed toward the composition of the test meals. The caloric makeup of the low saturated fat meal consisted predominately of high oleic sunflower oil, an oil designed to be lower in omega-6 fatty acids and higher in monounsaturated fats compared to traditional sunflower oils. Regardless of the different fat sources, it would be a stretch to call either meal healthy. Although anti-inflammatory diets emphasize the incorporation of healthy fats, a number of other aspects contribute to their health-promoting properties. Unfortunately, the meal with a perceived healthy fat content still contained highly refined carbohydrates with little fiber and no plant-based phytonutrients. It is unclear whether inflammation levels would still be elevated as a result of stress exposure after a true anti-inflammatory meal.

Aside from the limitations surrounding the test meals, additional analysis would have been helpful to best interpret the results. Foremost, no mention was made regarding a power analysis and the ability to detect differences based on the sample size. The researchers acknowledged that had a larger sample size been used, differences might have been detected between cancer survivors and controls. Theoretically, cancer survivors would exhibit different responses to inflammatory triggers as a result of their cancer history and/or cancer treatment. In addition to a larger sample size with stronger sub-group analysis, variables evaluating how stress influences the metabolic response to food would have augmented the study. For example, postprandial elevation of lipids has been associated with increased inflammatory markers leading to endothelial dysfunction.[5]

Despite the limitations, the study certainly advances our understanding regarding the interconnectedness of stress and nutrition. Hopefully, future studies will evaluate ways to minimize the inflammatory response to food eaten during periods of stress, as the literature generally is lacking at present. In the meantime, the practice of mindful eating is a reasonable prescription that integrative practitioners should recommend to their patients. ■

REFERENCES

1. Salas-Salvado J, Garcia-Arellano A, Estruch R, et al. Components of the Mediterranean-type food pattern and serum inflammatory markers among patients at high risk for cardiovascular disease. *Eur J Clin Nutr* 2008;62:651-659.
2. Schwingshackl L, Hoffmann G. Mediterranean dietary pattern, inflammation and endothelial function: A systematic review and meta-analysis of intervention trials. *Nutr Metab Cardiovasc Dis* 2014;24:929-939.
3. Kiecolt-Glaser JK. Stress, food, and inflammation: Psychoneuroimmunology and nutrition at the cutting edge. *Psychosom Med* 2010;72:365-369.
4. Blankenberg S, Barbaux S, Tiret L. Adhesion molecules and atherosclerosis. *Atherosclerosis* 2003;170:191-203.
5. O'Keefe JH, Gheewala NM, O'Keefe JO. Dietary strategies for improving post-prandial glucose, lipids, inflammation, and cardiovascular health. *J Am Coll Cardiol* 2008;51:249-255.

DEPRESSION

ABSTRACT & COMMENTARY

Physical Activity 'Moves' Teens Away from Depression

By Ellen Feldman, MD

Altru Health System, Grand Forks, ND

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

SYNOPSIS: Physical exercise may alleviate symptoms of depression in adolescents.

SOURCE: Carter T, Morres ID, Meade P, Callaghn P. The effect of exercise on depressive symptoms in adolescents: A systematic review and meta-analysis. *J Am Acad Child Adolesc Psychiatry* 2016;55:580-590.

Untreated depression in teens can affect quality of life for years. The developmental tasks of adolescence include the ability to make and sustain social relationships, develop a capacity for delayed gratification, and navigate the complex task of separation from parents; these all may be slowed or skewed by the weight of depressive symptoms.[1] Treatment of this highly prevalent disorder (approaching 20% of teens ages 13-20) is essential and typically involves a multimodal approach of medication, adjunct therapies, and lifestyle interventions.[2]

Carter et al investigated the effect of exercise in treating depressive symptoms in teens by conducting a meta-analysis. To identify appropriate, well- designed, and relevant studies, they applied specific criteria including:
1. The study was conducted as a randomized, controlled trial investigating depression in teens between 13-17 years of age.
2. The study incorporated physical activity as an intervention.
3. The publication was in English between the years of 1982 and 2015.
4. The study included baseline, control, and outcome results measuring depression.

CHARACTERISTICS OF THE STUDIES INCLUDED IN THE META-ANALYSIS

Eleven studies meeting all inclusion criteria were identified; out of these studies, eight had sufficient data to analyze and calculate effect size. A total of 384 individuals (from the eight studies) were involved in the meta-analysis; median sample size was 60; most were mixed sex; the mean age of the teens in each trial was between 14.7-17 years of age. Recruitment strategies for the studies varied from obtaining volunteers from a general high school population to more rigid inclusion of teens in a clinic population diagnosed with depression to teens diagnosed with depression on inpatient units. Thus, the severity of depressive symptoms at entrance to the studies varied widely.

Although all trials measured depression using self-report standardized scales, there was no consistent scale or measure used. The Children's Depression Inventory[3] was used in two of the eight studies; several other scales were employed in the other studies, including the Beck Depression Inventory (measuring depression and anxiety)[3] and the Beck Depression Scale.[4]

All trials included exercise at least three times weekly for 6-40 weeks, with a median duration of 11 weeks. The intensity of activity ranged from light to moderate, without any standard type or category of activity. Few trials looked at baseline level of exercise or activity or adjunct exercise (apart from the intervention during the study period).

Summary Points

- This is a comprehensive review and meta-analysis of randomized, clinical trials conducted between 1982 and 2015 regarding the effect of exercise on depression in teens.
- When looking at all eligible studies, exercise shows a moderate effect on decreasing depressive symptoms in adolescents.
- When narrowing the analysis to studies with participants diagnosed with depression (vs. a non-diagnosed, community-based population), the effect of exercise looks more substantial.

With recruitment, intervention techniques, and measurement tools differing trial to trial, the authors looked at several measures to determine the effect of exercise within the pooled samples. Among several other statistics, standardized mean difference (SMD) and level of heterogeneity were reported. The level of heterogeneity was thought to be particularly important to determine if comparable studies were being analyzed.

RESULTS

Table 1 represents analyzed results pooled and weighted from the eight studies. Table 2 shrinks the pool to the five studies that included only clinically depressed populations of teens. A lower depression score is indicative of less severity of depressive symptoms. Both study groups appear to show a moderate and statistically significant treatment effect from exercise on depressive symptoms. The lower heterogeneity (under 50%) for the clinical population lends more credibility to the concept that the studies are measuring the same intervention effect.

■ COMMENTARY

Adolescence is a period of change The negative implications of untreated depression during this time period can reach into the future; the effect of successfully treated depression in teens potentially is far-reaching. Adolescents with untreated depression are at higher risk for substance abuse, other psychiatric comorbidities, and suicide.[1,2,5] Most mental health professionals and medical providers agree that treatment of depression during adolescence is important, but a major dilemma and disagreement in treating this disorder lies in the specific modality

Table 1: Pooled Results for the Eight Studies Included in this Meta-analysis				
	Number of participants	SMD (standardized mean difference)	*P* value	Heterogeneity (I_2)
Experimental	220	-0.48	0.01	67%
Control	164			

Table 2: Clinical Sample and Pooled Results for the 5 Studies that Included Only Clinically Diagnosed, Depressed Study Participants				
	Number of participants	SMD (standardized mean difference)	*P* value	Heterogeneity (I_2)
Experimental	99	-0.43	0.04	44%
Control	84			

selected for intervention. The question is not should we treat, but *how* should we treat?

Many providers look to medication as a first step in treatment for adolescent depression. In the late summer of 2016, just after the publication of this meta-analysis looking at exercise and teen depression, another meta-analysis regarding treatment of depression in children and adolescents was published.[6] This second meta-analysis focused on treatment with antidepressant medication. From a pool of 34 trials and more than 5,000 participants, the researchers found that only fluoxetine was statistically more significant in terms of efficacy than placebo. In fact, the paper concluded:

"… considering the risk-benefit profile of antidepressants in the acute treatment of major depressive disorder, these drugs do not seem to offer a clear advantage for children and adolescents. Fluoxetine is probably the best option to consider when a pharmacological treatment is indicated."[6]

These two meta-analytic studies, while overlapping in some areas, cannot be compared head-to-head given significant differences, including age range of the participants, number of participants, and quality of the studies. However, it is worth reflecting that the relatively moderate effect of exercise on depressive symptoms rises in significance when viewed in the context of the results of the antidepressant studies.

As mentioned earlier, the standard of care in treatment of adolescent depression is multimodal.[3] Known side effects (including the "black box" warning regarding emergence of suicidal thoughts) and questions about the long-term effect of antidepressant medications on the developing brain concerns many parents, guardians, teens, and providers alike.[3,6] Non-pharmacologic therapies, including cognitive behavioral therapy, a specific type of talk therapy, have solid studies supporting efficacy, but geographical and financial barriers to well-trained therapists can make this treatment difficult to access.[7] Part of the excitement about exercise as an intervention is that it has few of these barriers and limited negative side effects.

However, one potential negative side effect is the concern that a teen may perceive that exercise alone should "fix" depression. It is quite important for providers to help patients and families understand these studies, the serious nature of untreated or undertreated depression, and various options for treatment. It also should be noted that positive side effects of exercise as a treatment for depression are numerous and include the full benefits of exercise on health in general.

This group of researchers set out to investigate the role of exercise in treatment of depressive symptoms in adolescence through a comprehensive meta-analysis. A survey of studies over a period of more than 30 years yielded only 11 adequate studies, and just eight of these had enough information to include in the meta-analysis. These numbers alone point to the need for better and more comprehensive, well-designed studies in this area.

Working with the information and data we have, it does appear that the results of this meta-analysis support exercise as an intervention to alleviate, at least partially, depressive symptoms, especially in adolescents with a diagnosis of depression. The evidence is not conclusive, but certainly is suggestive.

The degree to which symptoms are improved seems significant — even more so when we look at evidence for the efficacy of pharmacological treatments (as noted above).

Interestingly, the studies in the meta-analysis looked at symptom alleviation and not disease or disorder remission; there is no evidence from these studies regarding exercise as a standalone treatment in depression or in achieving full resolution of a depressive episode. Likewise, there is no evidence from these studies regarding using exercise as preventive intervention.

Unfortunately, the studies gave no concrete information regarding the presence or absence of any concurrent treatment for depression (pharmacological or other), leaving a clear knowledge gap regarding the role of exercise as an adjuvant treatment. Certainly, this is an area ripe for future investigation.

The impact and importance of a meta-analysis to understand the medical significance of an intervention grows in significance when few studies are available for analysis and when divergent methods and measurements exist. In this case, the results of the pooled analysis allow a provider more confidence in advising depressed teen patients to add exercise to a treatment regimen.

It is hopeful that another outcome of this meta-analysis will be that future researchers will pursue careful, well-designed studies to identify and categorize more precisely the role of exercise in treatment of depression. Knowing specifics about the type of activity needed (such as level of intensity needed, time-dependent criteria, group vs. individual activity) and gaining a more complete understanding of the mechanism of action during developmental stages will be helpful in clinical applications of this intervention.

For now, a provider is on solid ground letting depressed teens and guardians know it is likely that exercise plays a role in alleviation of depression symptoms. As symptom relief is achieved, the morbidity and mortality associated with teen depression is likely to remit as well. It appears that the risks associated with recommending exercise are slim and the potential gains great. Still, it remains prudent to caution patients that our knowledge about the role of exercise in depression is at an early stage and that effective treatment of depression usually involves multiple complementary interventions. Although exercise alone may not be the complete answer to teen depression, the evidence presented in this study suggests exercise can and should play a prominent role in treatment of this complex disorder. ■

REFERENCES

1. National Institute of Mental Health. Major Depression Among Adolescents. Available at: https://www.nimh.nih.gov/health/statistics/prevalence/major-depression-among-adolescents.shtml. Accessed Nov. 12, 2016.
2. ChildStats.gov. Adolescent Depression. Available at: http://www.childstats.gov/americaschildren/health2.asp. Accessed Nov. 12, 2016.
3. Stockings E, Degenhardt L, Lee YY, et al. Symptom screening scales for detecting major depressive disorder in children and adolescents: A systematic review and meta-analysis of reliability, validity and diagnostic utility. *J Affect Disord* 2015;174:447-463.
4. American Psychological Association. Beck Depression Inventory (BDI). Available at: http://www.apa.org/pi/about/publications/caregivers/practice-settings/assessment/tools/beck-depression.aspx. Accessed Nov. 22, 2016.
5. Thapar A, Collishaw S, Pine DS, Thapar AK. Depression in adolescence. *Lancet* 2012;379:1056-1067.
6. Cipriani A, Zhou X, Del Giovane C, et al. Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: A network meta-analysis. *Lancet* 2016;388:881-890.
7. Clarke G, DeBar LL, Pearson JA, et al. Cognitive behavioral therapy in primary care for youth declining antidepressants: A randomized trial. *Pediatrics* 2016;137:e20151851.

DIABETES

ABSTRACT & COMMENTARY

Extra-virgin Olive Oil Reduces Postprandial Glucose in Patients with Type 1 Diabetes

By Traci Pantuso ND, MS

Adjunct Faculty, Bastyr University, Seattle; Owner Naturopathic Doctor Harbor Integrative Medicine, Bellingham, WA

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

SYNOPSIS: In this study, the authors demonstrated significantly improved postprandial glucose levels in patients that consumed high glycemic index meals with extra-virgin olive oil compared to meals with butter or low fat meals.

SOURCE: Bozzetto L, Alderisio A, Giorgini M, et al. Extra-virgin olive oil reduces glycemic response to a high glycemic index meal in patients with type 1 diabetes: A randomized controlled trial. *Diabetes Care* 2016;39:518-524.

Bozzetto et al previously found that considering both the quality (fiber content) and quantity of carbohydrates, compared to only carbohydrate quantity, when calculating pre-meal insulin improves the daily blood glucose profile in type 1 diabetes (DM1) patients.[1] The use of continuous glucose monitoring in patients with DM1 has demonstrated that not only carbohydrate quantity but also protein and fat content affect postprandial glucose (PPG) levels.[2] There have been conflicting studies on how fat content in meals affects the PPG levels in patients with DM1. The aim of this study was to determine if there is an effect of different dietary fats on the PPG response to either a high glycemic index (HGI) or low glycemic index (LGI) meal.

Thirteen patients with DM1 (eight women and five men) were recruited at the University of Naples Federico II teaching hospital diabetes care unit in Italy. To be included in the study, the participants had to be undergoing treatment with continuous subcutaneous insulin infusion and fast-acting insulin analogs for the previous six months. Participants were excluded if they were pregnant, had a hemoglobin A1c (HbA1c) higher than 8.0%, suffered from serious micro/macrovascular complications, or had any other acute or chronic disease that seriously affected their health. Patients also were excluded if they had a diagnosis of celiac disease. The study design was a randomized, crossover trial with a one-week run-in period to provide baseline data. During the one-week run-in period, participants underwent continuous glucose monitoring (CGM) and completed a seven-day diet diary.

The HGI meals were composed of 60 grams of white rice, 75 grams of white bread, 90 grams of minced beef meat, and 180 grams of banana with the addition of the selected fat: butter (43 grams) or extra-virgin olive oil (EVOO) (37 grams) with 8 grams of EVOO in the low-fat meal. The LGI meals contained 50 grams of pasta, 100 grams of lentils, 30 grams of whole meal bread, 15 grams of ham, 185 grams of apple with either 45 grams of butter or 37 grams of EVOO, and 8 grams of EVOO in the low-fat meal.

Participants then were assigned by coin toss to a one-week period in which three lunchtime meals were consumed on three separate days that were either HGI or LGI. Then the participants were crossed over into the opposite glycemic index group. The participants underwent CGM throughout the study period and tested capillary postprandial blood glucose levels after the test meals at two, four, and six hours.

Summary Points

- The type of fat contained in meals may be more important than the quantity with respect to the effect on the postprandial glycemic response.
- Consuming 2.7 tablespoons of extra virgin olive oil combined in a high glycemic meal reduces the postprandial blood glucose levels compared to butter or low fat during the 0-3 hours after the meal.

Within each glycemic index group, there were three meal groups with different types of fat: low in fat, high in saturated fat (butter), or high in monounsaturated fat (EVOO).

Participants also underwent continuous glucose monitoring during the study period. A dietician supervised the preparation of the test meals, which were then frozen and given to the patients, who were instructed on how to defrost and heat them. The test meals were consumed at lunchtime between the second and seventh day of the CGM sensor life to prevent technical difficulties with the sensor. The prandial insulin doses were individualized per patient and were different between the HGI and LGI groups but were the same between the butter, EVOO, and low-fat meals.

ANOVA testing was used to evaluate the primary outcome of PPG incremental area under the curve (iAUC) between the different groups. The secondary outcomes evaluated were the blood glucose peak level and the time to the blood glucose peak.

The participants had an average HbA1c of 7.5 ± 1.0%; other characteristics are shown in Table 1. Two participants had background retinopathy and peripheral neuropathy, while one participant only had background retinopathy. One patient's PPG data were not included for the HGI group because of a technical issue with one of the CGM instruments.

Not unexpectedly, the PPG was significantly lower in the combined LGI meal group compared to the combined HGI meal group during the three hours after meal consumption (112 ± 62 vs. 337 ± 76 mmol/L x 180 min; $P = 0.006$). No significant difference was found in the three- to six-hour time frame between the combined HGI or LGI groups. There were no significant differences in blood glucose

Table 1: Participant Characteristics	
Characteristics	**Average ± SD**
Age	31 ± 11 years
Body mass index	24.8 ± 2.9 kg/m^2
Diabetes duration	25 ± 3 years
HbA1c	7.5 ± 1.0%
Total daily insulin dose	41.1 ± 10.7 IU

peak levels or time to blood glucose peak between the type and amount of fat in the LGI group.

In the HGI group, the PPG iAUC from 0-3 hours was significantly decreased in the EVOO meal compared to both the meal containing butter or the low-fat meal ($P < 0.05$). (*See Table* 2.) No significant differences were observed in PPG iAUC during the three- to six-hour time frame. The time to blood glucose peak for the EVOO group was statistically significantly delayed compared to the butter or lowfat meal groups ($P = 0.035$). The type and amount of fat did affect the iAUC in the HGI significantly. The high-fat EVOO meal decreased the PPG level significantly compared to the low-fat EVOO and butter meals ($P < 0.0001$). During the late postprandial phase, the low-fat meal group returned to fasting blood glucose levels, while the meal with butter demonstrated elevated blood glucose levels compared to fasting.

■ COMMENTARY

This study demonstrated that the type and amount of fat in HGI meals affects postprandial glucose during the 0- to 3-hour time but not in the late postprandial phase (3-6 hour). This is significant because DM1 patients maintain blood glucose levels through the use of insulin and calculating prandial insulin requirements, which is mostly based on calculating the amount of carbohydrates. The American Diabetes Association recommends that further education on the glycemic impact of fat and protein be provided after patients have mastered carbohydrate counting.[3] In a recent systematic review, the authors concluded that higher-fat meals require more insulin coverage than lower-fat meals with the same carbohydrate content.[2] This research study demonstrated that the effect of fat on PPG depends on the type of fat consumed and that monounsaturated fats, such as EVOO, may improve PPG levels compared to saturated fats such as butter, which affects overall insulin requirements. There was no significant effect of fat on PPG found in the LGI group.

Table 2: Postprandial Blood Glucose (0-3 hours) Levels in Participants Consuming HGI Meals with EVOO, Butter and Low Fat	
HGI Meal type of Fat	**Blood glucose iAUC 0-3 hours**
EVOO	198 ± 274
Butter	398 ± 355
Low fat	416 ± 329

The strengths of this study are the randomized, controlled, crossover trial design. Further, the authors also performed a power calculation that predicted 13 participants were needed to detect an 80% power and a 5% significance level for this study. The limitations of this study were the short duration and the lack of an EVOO biochemical profile. The study was performed in Naples, Italy, where access to high-quality EVOO may be greater than in the United States. However, the European Union top 10 foods at risk for food fraud listed olive oil as the highest risk.[4] In the United States between 1980-2012, oils have been rated the top category of fraudulent foods.[4] The main source of fraud with olive oil is the substitution of a lower cost alternative of either olive oil or, in certain cases, another nut or seed oil than what the label designates.[4] The International Olive Council provides guidelines for standards, both sensory and chemical, to assess olive oil quality. EVOO is considered the top grade of olive oil followed by virgin olive oil, refined olive oil, and olive oil, which is a blend of refined and virgin olive oil.

The United States is not a member of the International Olive Council. To further understand the quality of olive oil in the United States, the Olive Center at the University California, Davis published a report in 2011 investigating the quality of olive oils sold in California.[5] They concluded that 73% of the oils from the imported EVOO top five U.S. brands failed the International Olive Council's sensory panel test and 70% failed the chemistry test investigating the content of the 1,2 diacylglycerol and pyropheophytins.[5] A higher 1,2 diacylglycerol content in olive oil is an indicator of its better quality and freshness, while a higher pyropheophytins content indicates increased oxidization or adulteration with refined oil.[5] When recommending olive oil, it is important to counsel patients on the importance of using a good quality EVOO instead of buying the most cost-efficient type. This can be challenging, but there are a number of resources available to assist with the purchasing of quality EVOO.[6]

An estimated 1 million Americans have been diagnosed with DM1. Commonly diagnosed in childhood, adolescence, or early adulthood, DM1 is a chronic condition that is associated with micro/macrovascular and neuropathic complications. Maintenance of normal blood glucose levels with insulin greatly reduce the development and progression of DM1 complications.

This research study shows that LGI meals have better PPG levels than HGI meals and that the types and quantity of fats adds little to no extra benefit in LGI meals. The amount of carbohydrates is still the most important variable for PPG levels. However, it is possible to mitigate the adverse effects on PPG levels of HGI meals with EVOO, and even low-fat is better than high saturated fat. The results from this study illustrate some advice for patients with DM1, including an emphasis on LGI meals, the addition of high quality EVOO to HGI meals, and the reduction of dietary intake of saturated fats. ■

REFERENCES:

1. Bozzetto L, Giorgini M, Alderisio A, et al. Glycaemic load versus carbohydrate counting for insulin bolus calculation in patients with type 1 diabetes on insulin pump. *Acta Diabetol* 2015;52:865-871.
2. Bell KJ, Smart CE, Steil GM, et al. Impact of fat, protein and glycemic index on postprandial glucose control in type 1 diabetes: Implications for intensive diabetes management in the continuous glucose monitoring era. *Diabetes Care* 2015;38:1008-1015.
3. American Diabetes Association: Approaches to glycemic treatment. Sec.7 In Standards of Medical Care in Diabetes-2015. *Diabetes Care* 2015;38(Suppl 1):S41-S48.
4. Johnson R. Food Fraud and "Economically Motivated Adulteration" of Food and Food Ingredients. Congressional Research Service; 2014. Available at: https://fas.org/sgp/crs/misc/R43358.pdf. Accessed Dec. 1, 2016.
5. Frankel EN, Mailer RJ, Wang SC, et al. Evaluation of extra-virgin olive oil sold in California. UC Davis Olive Center at the Robert Mondavi Institute; 2011. Available at: http://olivecenter.ucdavis.edu/research/files/report041211finalreduced.pdf. Accessed Dec. 1, 2016.
6. Truth in Olive Oil. Available at: http://www.truthinoliveoil.com/. Accessed Dec. 1, 2016.

DIABETES

SHORT REPORT

Is Low Vitamin D Status Connected to an Increased Risk of Type 2 Diabetes?

By David Kiefer, MD, Editor

SYNOPSIS: In Greenland Inuit, increasing serum hydroxyvitamin D3 was associated with a worsening of physiological measurements and definitions of glucose homeostasis, contrary to what was expected.

SOURCE: Nielsen NO, Bierregaard P, Ronn PF, et al. Associations between vitamin D status and type 2 diabetes measures among Inuit in Greenland may be affected by other factors. *PLoS One* 2016;11:e0152763.

Sometimes, important discoveries in science begin with a perceived association between a variable (or variables) and an outcome, which leads to hypothesis generation, and more definitive testing. Along this vein, an intriguing story is developing between vitamin D and various physiological effects and clinical conditions, not the least of which is the possible connection between low serum vitamin D levels and type 2 diabetes. There has been a range of research trials investigating this, from epidemiological analyses to prospective cohort studies, and just as wide a range of results, but the connection remains dubious. Realizing that there was an opportunity to improve on the data, the researchers of the study being reviewed here mention both the methodological flaws of previous research and a unique population that they were able to study. With respect to the former, previous studies had sometimes just relied on dietary vitamin D intake to estimate levels, but that leaves out the crucial sunlight component. In addition, trials have relied on diabetes self-report, not always the most accurate way to corroborate that diagnosis. Which leads, then, to the demographic of focus for this study, the Inuit in Greenland.

Summary Point

- Fasting and non-fasting blood samples of Inuit in Greenland were used to demonstrate a positive association between vitamin D status and laboratory and clinical parameters such as fasting glucose, hemoglobin A1c, impaired glucose tolerance, and type 2 diabetes.

The Greenland Inuit have seen an increase in type

Table 1: Percentages of People with Impaired Glucose Metabolism			
	Impaired fasting glycemia (IFG)	**Impaired glucose tolerance (IGT)**	**Type 2 diabetes (DM2)**
Definition	Fasting plasma glucose 6.1-6.9 mmol/L, AND a 2-hour plasma glucose < 7.8 mmol/L	Fasting plasma glucose < 7.0 mmol/L, AND a 2-hour plasma glucose ≥ 7.8 mmol/Land <11.1 mmol.L	Fasting plasma glucose ≥ 7.0 mmol/L, OR a 2-hour plasma glucose ≥ 11.1 mmol/L
Percentage of cohort with this condition	13%	5.3%	8.8%

2 diabetes and "low" levels of vitamin D, as per citations offered by the authors. These changes are thought to be caused, in part, by an erosion of their traditional diet, which had been high in vitamin D from sea mammals and fish. Another characteristic of the Greenland Inuit is the fact that, due to the high latitude (minimal sunlight) and cold temperatures necessitating protective clothing, for much of the year the sunlight that is present provides little to no skin conversion of vitamin D. The researchers postulated that this would be the perfect population in which to show an association between vitamin D and diabetes.

[How do we interpret findings that were opposite the expectation? … Perhaps this is a lesson in the clinical limitations of statistical associations, as much as it is to embrace the wonder of science when results don't turn out quite as you would expect.]

A random sampling of permanent Greenland residents (90% of whom are Inuit) yielded 3,108 Inuit for this study, although only 2,877 had blood testing results available from 2005-2010. In addition, blood tests were available from 1987 (and then frozen until the present day; n = 330). This blood was tested for fasting glucose and insulin. In addition, a two-hour oral glucose tolerance test was administered; another blood sample was taken after 75 g of glucose was ingested. Blood also was analyzed for serum 25-hydroxyvitamin D3 (vitD), and hemoglobin A1c. At the time of the blood collections in 2005-2010, information about possible confounders was collected, including ancestry, exercise, smoking, and use of supplements; this information was not available for the 1987 samples.

The median vitD for the 1987 sample was 59.0 nmol/L, and for the 2005-2010 sample was 46.6 nmol/L. See Table 1 for the percentage of people with various types of impaired glucose metabolism. After adjusting for the confounders, interestingly increasing vitD by 10 nmol/L actually *increased* glucose by 0.03 mmol/L, two-hour glucose by 0.06 mmol/L, and hemoglobin A1c by 0.51%. Furthermore, increasing vitD decreased beta-cell function by 0.82%, a calculation not detailed here. With respect to glucose metabolism, the 2005-2010 samples showed that increasing vitD by 10 nmol/L increased the adjusted odds of impaired fasting glucose by 10%, and 7% for type 2 diabetes; no association was seen for impaired glucose tolerance. No statistically significant associations were seen for the 1987 samples.

How do we interpret findings that were opposite the expectation? The mechanism from other research groups does not support that vitamin D would have an adverse effect on type 2 diabetes parameters. The authors believe these results and implicate "other factors" that might be involved. That may be true, and, if anything, it prompts a continued search to define the physiological actions of vitamin D and its metabolites. At least, as the authors said, the effects on impaired fasting glucose, impaired glucose tolerance, and type 2 diabetes risk is "… of limited clinical importance." The changes seen were minimal, thankfully, but still enough to make clinicians pause before globally recommending vitamin D supplementation for all patients with, or at risk for, type 2 diabetes or metabolic syndrome. Perhaps this is a lesson in the clinical limitations of statistical associations, as much as it is to embrace the wonder of science when results don't turn out quite as you would expect. ■

SHORT REPORT

Cardiorespiratory Fitness May Stave Off the Development of Depression

By David Kiefer, MD, Editor

SYNOPSIS: Lower cardiorespiratory fitness increases the risk of developing depression in adults.

SOURCE: Schuch FB, Vancampfort D, Sui X, et al. Are lower levels of cardiorespiratory fitness associated with incident depression? A systematic review of prospective cohort studies. *Prev Med* 2016;93:159-165.

In this issue, we are featuring a couple of articles on exercise, both because of their timely publication as well as the setting of yearly resolutions for lifestyle change. In addition, both of these articles explore the connection between exercise and depression, the latter being a challenge for some people during the long winter nights and waning light. Perhaps patients in our clinical practices can benefit from some of the interesting results featured in this issue.

Using a systematic review research methodology, Schuch et al saved clinicians the task of having to review individual clinical trials themselves. The authors justified exploring cardiorespiratory fitness (CRF), which they defined as "… the ability of the circulatory and respiratory systems to supply oxygen to working muscles during sustained physical activity, typically expressed as mL O_2/kg-1/min-1 … ," because of some prior work supporting its effect on human health as much or more than the more generic variable, physical activity (the authors provided some references to this effect). In this review, the researchers found three CRF clinical trials, and used two of them to generate data for this analysis; the third study did not include a hazard ratio (HR), precluding its inclusion in the pooling of data. The adult study participants did not have a mental health condition diagnosed at baseline. In addition, the clinical trials were prospective in design, and had at least one year of follow-up. Studies also had to have the primary outcome as either the risk (odds) of developing depression, or "… the association between cardiorespiratory fitness and depression or depressive symptoms."

Summary Point

- Low and medium cardiorespiratory fitness are associated with a 76% and 29% higher risk, respectively, of adults developing depression.

The characteristics of the two included studies are shown in Table 1. Overall, the pooled analysis included data on 1,131,330 people. A higher risk ($P < 0.001$) of developing depression was demonstrated in those adults with low CRF (hazard ratio [HR], 1.76; 95% confidence interval [CI], 1.61-1.91) and medium CRF (HR, 1.29; 95% CI, 1.20-0.138). The authors interpret these results as evidence that "… interventions that specifically target CRF might also promote positive mental health outcomes." However, there are caveats. This is merely an observation study, so causation can't be implied; for example, we are not able to say that low CRF *causes* depression. Furthermore, few details were provided of the methods that CRF was measured, other than the fact that the studies did not use the "gold standard" VO_{2max}. Future studies that standardize this measurement would do much to help clinicians know exactly what to tell patients about how long, what type, and how intense exercise would benefit their mental health. Obviously, more studies are needed (just two were included here), but the number of patients studied in this analysis was impressive. In addition, the authors did not include the results of the high CRF groups, so any implication that more exercise leads to a lower risk of depression

Table 1: Characteristics of the Studies

Author	Number of study participants	Years of follow up	Location	Demographic	Demographic
Aberg et al.	1,117,292	3-40	Sweden	Military	Men
Sui et al.	14,038	10-11	United States	Community	Men and women

would be merely conjecture. Going forward, there is little reason for clinicians not to help patients move (pun intended) away from being in the low and medium CRF groups, no matter how that is defined, and it may also benefit their mental health. ■

CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:

1. Read and study the activity, using the references for further research.
2. Scan the QR code to the right or log on to AHCMedia.com and click on My Account. First-time users will have to register on the site using the eight-digit subscriber number printed on the mailing label or invoice.
3. Pass the online test with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After completing the test, a credit letter will be emailed to you instantly.
5. Twice yearly after the test, your browser will be directed to an activity evaluation form, which must be completed to receive your credit letter.

CME QUESTIONS

1. **What did the meta-analysis examining depression and exercise in teens reveal?**
   a. A threshold of exercise above which no further benefits regarding depression were noted.
   b. Teen depression most likely can be treated with exercise alone, as long as there is sufficient duration and intensity of physical activity.
   c. Teen depression requires multiple intervention modalities; exercise is effective only when combined with medication or therapy.
   d. Symptoms of depression in teens may be affected favorably by exercise.

2. **Which of the following is true regarding extra virgin olive oil (EVOO)?**
   a. EVOO is the highest quality olive oil and high level of pyropheophytins is indicative of high quality.
   b. EVOO is the highest quality olive oil and high level of 1,2 diacylglycerols is indicative of high quality.
   c. EVOO that is sold in the United States is unlikely to be adulterated.
   d. The United States is a member of the International Olive Council.

3. **Which of the following was associated with increasing serum hydroxyvitamin D3 values in the Greenland Inuit?**
   a. A decrease in hemoglobin A1c
   b. An increase in 2-hour glucose
   c. A decrease in fasting glucose
   d. Lower risk of impaired fasting glycemia

4. **Which of the following was found by Schuch et al as an association with low cardiorespiratory fitness?**
   a. A 33% lower risk of developing depression
   b. A 76% higher risk of developing depression
   c. A 76% lower risk of worsening depression
   d. A 76% higher risk of depression resolving

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- present evidence-based clinical analyses of commonly used alternative therapies;
- make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and
- describe and critique the objectives, methods, results, and conclusions of useful, current, peer-reviewed, clinical studies in alternative medicine as published in the scientific literature.

[IN FUTURE ISSUES]

Omega-3 fatty acids after myocardial infarction

Religious attendance and suicide rates

Coenzyme Q10 and Parkinson's disease

Beetroot juice and endurance