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ABSTRACT & COMMENTARY

Diet High in Carbohydrates, Not Fats, Drives Mortality

By Joseph E. Scherger, MD, MPH

Vice President, Primary Care, Eisenhower Medical Center; Clinical Professor, Keck School of Medicine, University of Southern California, Los Angeles

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

SYNOPSIS: A prospective epidemiological cohort study of people 35-70 years of age in 18 countries showed that a higher intake of carbohydrates increased total mortality, while the intake of fats of all kinds did not. A higher intake of saturated fat reduced stroke mortality.

SOURCE: Dehghan M, Mente A, Zhang X, et al. Association of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): A prospective study. *Lancet* 2017 Aug 28. pii: S0140-6736(17)32252-3. doi: 10.1016/S0140-6736(17)32252-3. [Epub ahead of print].

The evidence is mounting that fats, including saturated fats from natural food sources, are not associated with cardiovascular or total mortality. Rather, high carbohydrate intake is associated with earlier mortality.

This large epidemiological study was performed prospectively with individuals 35-70 years of age enrolled starting in 2003 and followed for 5.9-9.3 years. The study included 135,000 individuals from 18 countries on five continents. There were 5,796 deaths and 4,784 major cardiovascular events. Higher carbohydrate intake was associated with greater total mortality (hazard ratio [HR], 1.28), and greater fat intake (all types of fats) was associated with lower mortality (HR, 0.77). There was no association between fat intake and cardiovascular disease, myocardial infarction, or cardiovascular mortality. Stoke rate also was lower in the high fat group (HR, 0.79).

■ COMMENTARY

Reanalysis of the information used to promote a low-fat diet was not based on good science.[1] The sugar industry, wanting to avoid negative press on its products, played a major role in funding

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the effort to reduce fat intake.[2] We are recovering from this misinformation, with leading academic investigators taking a stand and educating the public.[3-5]

All physicians should advise their patients to eat real food from nature without food labels as much as possible. Highly processed foods, especially grains and sweets, should be avoided. That is difficult since we have created a culture around cookies, cakes, candy, and pizza. The food industry is resisting this change, similar to how the tobacco industry behaved in the past. Physicians should be role models and champions of healthy eating. ■

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ABSTRACT & COMMENTARY

Mother Was Right: You Are What You Eat

By Seema Gupta, MD, MSPH

Clinical Assistant Professor, Department of Family and Community Health, Joan C. Edwards School of Medicine, Marshall University, Huntington, WV

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

SYNOPSIS: In a study of simplified enterotypes as prognostic markers for successful body fat loss on two different diets, participants with a greater ratio of *Prevotella* to *Bacteroides* appeared more susceptible to lose body fat on diets high in fiber and whole grains.

SOURCE: Hjorth MF, Roager HM, Larsen TM, et al. Pre-treatment microbial Prevotella-to-Bacteroides ratio, determines body fat loss success during a 6-month randomized controlled diet intervention. *Int J Obes (Lond)* 2017 Sep 8. doi: 10.1038/ijo.2017.220. [Epub ahead of print].

The human gut contains a complex microbial community of microorganisms known collectively as the "gut microbiota," which interacts with and influences one's health status. As a densely populated bacterial collection, with approximately 1,011 organisms per gram of fecal weight, the human gut microbiota is composed of more than 1,000 species, most of which are obligate anaerobes.[1] The assessment and characterization of this gut microbiota has become a major research area in human disease, including obesity and type 2 diabetes mellitus (T2DM), illnesses that represent two of the greatest global health challenges of this century associated with significant comorbidities and healthcare costs. Although several factors contribute to the development and progression of obesity and T2DM, in recent years metagenome-wide association studies have revealed potential relationships between intestinal microbiomes and the pathogenesis of T2DM.[2,3] The gut microbiota can contribute to human health in multiple ways, including roles in polysaccharide breakdown, nutrient absorption, inflammatory responses, bile acid modification, and gut permeability. Although numerous studies have suggested that disruptions in the relative proportions of gut microbial populations may contribute to weight gain and insulin resistance, most of these studies are conducted with stool or colonic samples and have not compared the relative efficacy of various weight loss diets in relation with the gut microbiota.[4] The human gut microbiota has been grouped into three distinct categories of enterotypes based on a relatively high abundance of

Bacteroides species (enterotype 1), *Prevotella* species (enterotype 2), and *Ruminococcus* (enterotype 3). Research suggests enterotypes 1 and 2 may be associated with long-term diets within individuals. Enterotype 1 is reported to be predominant in individuals consuming Western diet (more protein and animal fat), whereas enterotype 2 appears predominant in those who consume more carbohydrates and fiber.[5]

As a proxy for enterotypes, Hjorth et al studied the pretreatment *Prevotella*/*Bacteroides* ratio (P/B ratio) as a prognostic marker for successful body fat loss on two diets differing greatly in dietary fiber and whole grain content. Researchers randomly assigned 62 participants with increased waist circumference to receive an ad libitum New Nordic Diet (NND, a fiber-rich option that places more emphasis on whole foods such as vegetables and fruits) or an Average Danish Diet (ADD, which includes lean meat, coffee, lettuce, and eggs without grains) for 26 weeks. Participants' weight and body measurements were taken before and after they started the 26-week diets. They were grouped into two discrete enterotypes by the relative abundance of *Prevotella* species divided by *Bacteroides* species (P/B ratio) obtained by quantitative polymerase chain reaction analysis of their stool samples. After the initial 26-week study period, all 62 participants followed the NND for another year.

Researchers found that among individuals with a high P/B ratio, the NND resulted in a 3.15 kg (95% confidence interval [CI], 1.55-4.76; $P < 0.001$) larger body fat loss compared to ADD, whereas no differences was observed among individuals with low P/B ratio (0.88 kg; 95% CI, 0.61-2.37; $P = 0.25$). Consequently, a 2.27 kg (95% CI, 0.09-4.45; $P = 0.041$) difference in response to the two diets was found between the two P/B groups. In essence, study participants who demonstrated a high P/B ratio appeared more likely to lose body fat on diets high in fiber and whole grain when compared to subjects who exhibited a low P/B ratio. Their waistlines also decreased more significantly. Interestingly, during the one-year follow-up period, a 3.99 kg (95% CI, 1.82-6.15; $P < 0.001$) difference in responsiveness to the NND was found between the two P/B groups.

■ COMMENTARY

We are what we eat. Everyone has heard it, but most probably don't quite believe it. A growing body of literature suggests that diet, and not the obese state, may be the major driving force behind gut microbiota changes.[6] In fact, the effect of diet on the composition of the gut microbiota begins early in life. As these human intestinal bacteria are linked to the increasing prevalence of overweight and obesity, scientists have started to investigate whether the intestinal bacteria can play a role in the treatment of overweight, obesity, and diabetes. Therefore, while it may be frustrating for our patients attempting to lose weight by trying various weight loss diets, research into the predominant type of human gut microbiota may play an increasing role in helping personalize nutrition, including the recommendation for particular types of diets. We have explored the effectiveness of various weight loss diets based on effects on energy expenditure, body weight, body composition, and metabolic parameters. However, it is becoming clearer that certain bacterial species and imbalances in one's gut may play a decisive role in weight regulation and loss. Restoring those imbalances in gut bacteria by dietary modifications may be the answer to addressing one of the biggest global public health crises. Clinicians may soon recommend that patients submit a stool sample to determine if they're able to lose weight on a personalized diet based on the results. ■

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ABSTRACT & COMMENTARY

Is a Dabigatran Reversal Agent Effective?

By Michael H. Crawford, MD

Professor of Medicine, Chief of Clinical Cardiology, University of California, San Francisco

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

SYNOPSIS: A pragmatic clinical study of idarucizumab for counteracting the effects of the oral anticoagulant dabigatran showed rapid and complete reversal of its effects in patients with major bleeding or urgent surgery, without any adverse safety concerns.

SOURCE: Pollack CV Jr, Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal – full cohort analysis. *N Engl J Med* 2017;377: 431-441.

One advantage of dabigatran therapy for stroke prevention in atrial fibrillation (AF) patients is the existence of an antidote, but how well does it work? Investigators performed a multicenter, international, prospective, open-label study of idarucizumab 5 mg IV in 503 patients on dabigatran needing anticoagulant reversal, the Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) study. The authors studied two groups of patients. Group A had life-threatening bleeding (n = 301). Group B required surgery and couldn't wait eight hours for hemostasis to return after stopping dabigatran (n = 202). The primary endpoint was the maximum percent reversal of anticoagulation four hours after completion of the infusion of idarucizumab as measured by either the thrombin time or the ecarin clotting time. Serial blood samples for pharmacologic studies were performed over the first 24 hours after the infusion of idarucizumab. A second dose of idarucizumab was permitted for recurrent or continued bleeding or objective evidence of residual anticoagulant effect. Clinical outcomes were secondary endpoints. Adverse effects were attributed to idarucizumab if they occurred within five days. More than 95% of the patients were receiving dabigatran for stroke prevention in AF. The mean age was 78 years. The median percent reversed at four hours was 100%. Dabigatran concentrations fell from around 100 mg/mL to near zero within minutes of the infusion of idarucizumab and remained < 20 mg/mL for 24 hours. A second dose of idarucizumab was administered to only eight patients. In group A, 46% experienced gastrointestinal bleeding, and 33% experienced intracranial bleeding. The median time to cessation of bleeding was 2.5 hours after idarucizumab was administered. In group B, the planned surgery commenced at a median time of 1.6 hours. Perisurgical hemostasis was normal in 93%. At 90 days, about 7% of patients experienced a thrombotic event and 19% experienced mortality. There were no serious safety issues with idarucizumab administration. The authors concluded that idarucizumab was shown to rapidly reverse the anticoagulation caused by dabigatran without any serious safety issues.

■ COMMENTARY

Although idarucizumab worked well in animals and normal volunteers to reverse the effects of dabigatran, it is always useful to see how such agents work in real-world patients. Thus, this uncontrolled, pragmatically designed, open-label study is of interest. Clearly, idarucizumab rapidly drops dabigatran blood levels to near zero for at least 12 hours. Between 12 and 24 hours, some anticoagulant effect (dabigatran levels < 20 mg/mL) returned in about 20% of patients. The authors attributed this to the redistribution of dabigatran from extravascular spaces into the vasculature. This was associated with bleeding in only 10 patients. A second dose of dabigatran was administered to seven of these patients. Overall, only one dose of 5 mg of idarucizumab was given to 98% of patients. Anti-idarucizumab antibodies were detected in about 6% of patients, but at low titers. Three patients demonstrated possible hypersensitivity events: one with a rash who also started tramadol; one with vomiting and loss of consciousness who had intracerebral hemorrhage; and one with possible anaphylaxis who was started on amoxicillin. Other potential adverse events were observed in about one-quarter of patients, but all could be ascribed to worsening of the index event or the underlying condition of the patients.

In group B, the surgeons reported 95% of patients appeared to exhibit normal or mildly impaired hemostasis at a median start time of 1.6 hours after idarucizumab was administered. Considering these data and the safety of idarucizumab, surgery probably could start as soon as the idarucizumab is administered. In group A, the efficacy of idarucizumab is more difficult to determine. These were sick patients with a high mortality rate (7% at five days, 13% at 30 days). Also, there were many factors affecting hemostasis. Often, blood transfusions occurred and other products were administered. In addition, many received antiplatelet agents at a mean of four days, and most restarted anticoagulants at a mean of 13 days. Investigators started such agents within 72 hours in 23% of group A patients. Further, the authors noted that mortality reported in patients undergoing surgery

or experiencing a major spontaneous bleeding event on warfarin is about 30%, which is higher than the 19% observed in this study. Finally, thrombotic events are to be expected if one rapidly reverses anticoagulation, but the 7% observed in this study is lower than that reported with warfarin. No procoagulant effect of idarucizumab has been observed in animals or normal human volunteers. Since there is no effective alternative to idarucizumab for reversing the effects of dabigatran, there was no comparison group, and the investigators believed that it was unethical to create a control group given the strength of the pre-clinical data. The FDA has approved idarucizumab at the doses used in this study. This makes dabigatran an attractive oral anticoagulant for patients who demonstrate indications for oral anticoagulation but are at high risk of bleeding. ■

PHARMACOLOGY UPDATE

Meropenem and Vaborbactam Injection (Vabomere)

By William Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Assistant Clinical Professor of Medicine, University of California, San Francisco.
Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco.

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The FDA has approved a new combination antibacterial for the treatment of complicated urinary tract infections. The new antibacterial combines meropenem, a synthetic carbapenem available since 1996, and a new beta-lactamase inhibitor called vaborbactam. This is the second new beta-lactamase inhibitor to be approved after avibactam, which is combined with ceftazidime (Avycaz). Meropenem/vaborbactam was designated as a qualified infectious disease product and received a priority review. It is marketed as Vabomere.

INDICATIONS

Meropenem/vaborbactam is indicated for treating patients ≥ 18 years of age with complicated urinary tract infection (cUTI), including pyelonephritis caused by susceptible bacteria from the Enterobacteriaceae family of gram-negative bacteria.[1] These include *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae* species complex.

DOSAGE

The recommended dose for adults is 4 grams (meropenem 2 grams and vaborbactam 2 grams) administered through an IV infusion (over three hours) every eight hours for up to 14 days.[1] The dose should be reduced based on the degree of renal impairment (i.e., estimated glomerular filtration rate). Vabomere is available as 2 gram single-dose vials containing 1 gram each of meropenem and vaborbactam.

POTENTIAL ADVANTAGES

Vaborbactam, similar to avibactam, is a potent inhibitor of serine Ambler class A and class C beta-lactamases, with potent activity against *Klebsiella pneumoniae* carbapenemase (KPC)-producing bacteria and other class A carbapenases.[2] Older beta-lactamases such as clavulanic acid, sulbactam, and tazobactam, do not inhibit class A carbapenemases.

POTENTIAL DISADVANTAGES

Meropenem/vaborbactam is not active against bacteria that produce metallo-beta-lactamase or oxacillinases with carbapenemase activity.[1] Meropenem/vaborbactam reduces the concentration of valproic acid and divalproex sodium. Concomitant use is not recommended.[1] The most common adverse reactions were headache (8.8%) and phlebitis/infusion site reactions (4.4%).[1]

COMMENTS

The efficacy and safety of meropenem/vaborbactam were evaluated in a comparative, double-blind, double-dummy, clinical trial with 545 subjects with cUTI.[1,3] The FDA defines cUTI as a clinical syndrome characterized by local and systemic signs and symptom, including fever, chills, malaise, flank pain, back pain, and/or costovertebral angle pain or tenderness that occur in the presence of functional or anatomical abnormality of the urinary tract or in the presence of catherization.[4] Pyelonephritis is considered a subset of cUTI. Study participants primarily were Caucasian (93%), had a mean age of 54 years, and 59% had pyelonephritis. Subjects were randomized to meropenem/vaborbactam (2 grams each) or piperacillin (4 g/tazobactam 0.5g) every eight hours. Switching to an oral antibacterial was allowed after a minimum of 15 parenteral doses. Efficacy was evaluated by clinical and microbiological responses at the end of IV treatment and also at seven days after completion of treatment. The first assessment required clinical outcome of cure or improvement and an eradication

of baseline uropathogens. The second required clinical cure and microbiological eradication. A total of 186 subjects in the meropenem/vaborbactam group and 175 in the piperacillin/tazobactam group met the condition for analysis (received study drug and demonstrated at least one baseline uropathogen). Success rates at the end of IV treatment were 98.4% for meropenem/vaborbactam and 94.3% for piperacillin/tazobactam. At approximately seven days after treatment completion, rates were 76.5% vs. 73.2%. The first outcome met criteria for non-inferiority and superiority, and the second outcome met criteria for non-inferiority.[5]

CLINICAL IMPLICATIONS

Gram-negative bacteria of the Enterobacteriaceae family are a common cause of urinary tract infections.[2] They also are associated with antibiotic resistance by way of extended beta-lactamase production and carbapenem resistance. Vaborbactam is designed as a potent inhibitor of serine carbapenemases, particularly KPC.[6] Meropenem/vaborbactam provides a new option, and should be reserved for cUTI caused by KPC-producing Enterobacteriaceae. The Data and Safety Monitoring Board ended a second clinical trial early because of efficacy benefit over best available therapy in serious infections due to carbapenem-resistant Enterobacteriaceae in adults.[7,8] Best available therapy generally included aminoglycosides, polymyxin B, colistin, tigecycline, or various combination of these. Serious infections included cUTI, hospital-associated bacterial pneumonia, ventilator-associated bacterial pneumonia, and bacteremia. Meropenem/vaborbactam is expected to be available in the fourth quarter of 2017. Cost was not available at the time of this review. ■

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Clinical Briefs

By Louis Kuritzky, MD

Separating Celiac Disease From Non-celiac Gluten Sensitivity

SOURCE: Leonard MM, Sapone A, Catassi C, Fasano A. *JAMA* 2017;318:647-656.

The consequences of celiac disease include intestinal symptoms as well as diverse extraintestinal disorders such as anemia, osteoporosis, and increased risk of lymphoma. Gluten sensitivity has become sufficiently "popular" that an entire industry of "gluten-free" products has been created to satisfy the needs of a gluten-wary populace that too often views gluten as a toxin.

Patients with celiac disease possess specific human leukocyte antigen genotypes (DQ2 and DQ8) that allow an aberrant immunologic response to gluten-containing proteins, leading to the recognized signs and symptoms of celiac disease. Clinicians confirm the disease through intestinal biopsy. Consistently, this leads to not only symptom remission but also gluten antibody decline (anti-transglutaminase and antigliadin).

Anyone can experience a "food intolerance," unpleasant symptoms ranging from dyspepsia to diarrhea and beyond in response to individual foods. Most patients who experience an adverse symptom in response to a particular food simply choose to avoid that food in the future and do not label it "broccoli sensitivity syndrome" or "lima bean sensitivity syndrome."

Because adverse abdominal symptomatology is commonplace in otherwise healthy individuals periodically, and there is high public awareness of gluten as a cause of abdominal pain in celiac disease, some simply remove gluten from their diet after which adverse abdominal symptoms (or sometimes other symptoms) disappear. Many of these individuals believe they suffer from celiac disease and never undergo appropriate diagnostic testing to affirm the diagnosis.

As there is no diagnostic test to confirm any patient's "non-gluten celiac sensitivity," whether this clinical constellation should be considered a legitimate disorder remains a matter of controversy. However, there is no uncertainty about the necessity for long-term follow-up of patients with confirmed celiac disease. ■

BCG Vaccinations and the False-positive Effect

SOURCE: Mancuso JD, Mody RM, Olsen CH, et al. *Chest* 2017;152:282-294.

A placebo-controlled trial of bacille Calmette-Guerin (BCG) vaccination was performed among Native Americans from Alaska, Arizona, North Dakota, South Dakota, and Wyoming from 1935-1947. Varying opinions appear in the literature about the length of time during which prior BCG vaccination influences reactions to tuberculin skin testing. For instance, the CDC suggests that tuberculin cross-reactivity is unlikely to persist longer than 10 years post-BCG vaccination.

A publication by Mancuso et al offers us a 55-year follow-up of 3,151 subjects who received the BCG vaccines inclusive of up to 55 years post-BCG vaccination. In this population, within the first five years of follow-up, > 60% of BCG recipients registered positive tuberculin testing results.

Although this number waned somewhat over time (only 33% were positive after 50 years of follow-up), more than half of BCG vaccines remained tuberculin-positive throughout the initial 44 years of follow-up. Based on this data, clinicians should consider that the BCG vaccination effect could influence tuberculin testing responsivity for an essentially indefinite period. ■

Azithromycin Reduces Asthma Exacerbations

SOURCE: Gibson PG, Yang IA, Upham JW, et al. *Lancet* 2017;390:659-668.

In my early years of training, I was tempted occasionally to consider an antibiotic during an asthma exacerbation, but was quickly advised about the basic foolhardiness of such a consideration. After all, asthma exacerbations essentially are induced exclusively by viral infections (as well as thermal and atopic stimuli). Is it time to reconsider that posture?

In the AMAZES clinical trial, symptomatic adult asthmatics (n = 420) on a long-acting bronchodilator and inhaled steroid were randomized to azithromycin 500 mg thrice weekly vs. placebo for 48 weeks. The primary outcome was number of asthma exacerbations.

In a previous similarly designed trial of COPD patients receiving azithromycin 250 mg/day for one year, a decrement in hearing function was noted in the azithromycin treatment arm; hence, patients with any hearing impairment were excluded from this trial.

At 48 weeks, subjects on azithromycin experienced a 61% reduction in asthma exacerbations, as well as a statistically significant improvement in quality of life. Tolerability of azithromycin was very good, although diarrhea was twice as common in the azithromycin group as the placebo group (34% vs. 19%, respectively; $P < 0.05$).

The authors reminded us that macrolides, in addition to antibacterial effects, also possess anti-inflammatory and antiviral activity. ■

CME INSTRUCTIONS

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CME QUESTIONS

1. **High intake of what macronutrient is associated with a greater total mortality?**
   a. Saturated fats
   b. Polyunsaturated fats
   c. Proteins
   d. Carbohydrates

2. **Based on the results of the study by Hjorth et al, which statement is true regarding pre-treatment *Prevotella/Bacteroides* (P/B) ratio as a prognostic marker for successful body fat loss and various diets?**
   a. Individuals with a high P/B ratio were more susceptible to body fat loss on a diet rich in fiber and whole grains.
   b. Individuals with a low P/B ratio were more susceptible to body fat loss on a diet rich in fiber and whole grains.
   c. Individuals with a high P/B ratio were more susceptible to body fat loss on a diet rich in proteins.
   d. Individuals with a low P/B ratio were more susceptible to body fat loss on a diet rich in proteins.

3. **In patients on dabigatran who receive idarucizumab (a reversal agent), dabigatran blood levels fell to near zero within:**
   a. seconds.
   b. minutes.
   c. two hours.
   d. four hours.

CME OBJECTIVES

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

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages, and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

[IN FUTURE ISSUES]

Irritable Bowel Syndrome, Constipation, and Quality of Life in Women

Functional Outcomes After Receiving Life-sustaining Therapy in the ICU