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ABSTRACT & COMMENTARY

Eat Vegetables and Prevent Type 2 Diabetes

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

SYNOPSIS: A large meta-analysis of high-quality observational studies shows that adherence to a plant-based diet is inversely related with developing type 2 diabetes.

SOURCE: Qian F, Lie G, Hu FB, et al. Association between plant-based dietary patterns and risk of type 2 diabetes: A systematic review and meta-analysis. *JAMA Intern Med* 2019; Jul 22. doi: 10.1001/jamainternmed.2019.2195. [Epub ahead of print].

A group at the Harvard T.H. Chan School of Public Health reviewed several observational studies that met stringent epidemiological guidelines regarding associations between nutrition and type 2 diabetes. Qian et al used an assessment tool from the National Institutes of Health to assess the quality of the studies. Nine studies that included 307,099 participants (23,544 cases of type 2 diabetes) were used in this analysis. All data showed an inverse relationship between a plant-based diet and developing type 2 diabetes. A plants-only diet was not required to prevent diabetes.

■ COMMENTARY

The "elephant in the room" with respect to the growing epidemic of insulin resistance and type 2 diabetes is the consumption of sugar and refined carbohydrates.[1,2] Proponents of a whole food, plant-based diet like to point out the association of meat with the development of type 2 diabetes.[3,4] There is a biological basis for their argument, but they tend to ignore the preeminent role of sugar and refined carbohydrates in the development of type 2 diabetes. The truth is that sugar and other carbohydrates come from plants, not animal sources. The quality of the plants ingested is vital to this argument. People who eat spinach, broccoli, and kale tend to eat much healthier than those who eat burgers.

The importance of this study and other investigations of connections between nutrition and type 2 diabetes is that this most expensive of chronic illnesses is

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preventable. There is a genetic risk that must be considered, but overweight, obesity, insulin resistance, metabolic syndrome, and type 2 diabetes are a continuum of epigenetic problems. Helping patients eat healthy goes a long way in preserving and restoring health and the prevention and reversal of chronic disease. ■

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ABSTRACT & COMMENTARY

Blood Pressure Control: Exercise vs. Meds

By Eric Neilson, MD, and Nancy Selfridge, MD

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Drs. Neilson and Selfridge report no financial relationships relevant to this field of study.

SYNOPSIS: A random-effects network meta-analysis demonstrated comparable reductions in systolic blood pressure among normotensive and hypertensive participants using either antihypertensive medication or exercise interventions.

SOURCE: Naci H, Salcher-Konrad M, Dias S, et al. How does exercise treatment compare with antihypertensive medications? A network meta-analysis of 391 randomized controlled trials assessing exercise and medication effects on systolic blood pressure. *Br J Sports Med* 2019;53:859-869.

Hypertension is one of the most common causes of morbidity and mortality in the world. It is also modifiable. The 2017 American College of Cardiology and the American Heart Association guidelines have expanded the categories of hypertension to include people at risk of developing the disease and its associated complications, and recommend lifestyle modification, including exercise programs, as a key component in the treatment of each of these categories.[1]

In this network meta-analysis, Naci et al showed that the large amount of data available regarding systolic blood pressure (SBP)-lowering effects of antihypertensive medications are quite consistent. Although research evidence on the effect of exercise is more limited and variable, it can be as effective at reducing SBP, especially in patients with hypertension. Naci et al analyzed pooled data from recently published meta-analyses and randomized, controlled trials (RCTs) of exercise or antihypertensive medication effects on SBP. Exercise intervention trials included endurance, dynamic resistance, isometric resistance, or combinations of endurance and dynamic resistance lasting at least four weeks. Medication intervention eligibility was based on the British National Formulary dosing criteria and included studies of angiotensin-converting enzyme inhibitors (ACE-I), angiotensin-2 receptor blockers (ARB), β-blockers, calcium channel blockers (CCB), or diuretics. Mean SBP changes with a 95% confidence interval were calculated for each treatment modality, and comparison data were compiled.

Overall, both exercise and medication interventions lowered SBP. When comparing different types of exercises, endurance, isometric resistance, and a combination showed the greatest improvements in SBP. Variations in intensity did not demonstrate statistically significant differences. The largest medication

decreases in SBP were from CCB classes. Among patients with hypertension, reductions were greatest in the combination exercises group and outperformed the largest medication reductions by an average of between 1 mmHg and 3 mmHg.

Limitations of the review, affecting its internal validity, primarily reflected limitations in the original studies. These included significant heterogeneity within the exercise studies, limitations in reporting, and methodological flaws (e.g., small sample sizes, lack of blinding of investigators and participants in exercise trials, blood pressure change as a secondary or tertiary outcome for many of the exercise studies).

Upon conclusion of the analysis, the authors noted the need for more robust research consisting of larger-scaled, well-designed studies comparing the effectiveness of antihypertensive medication directly to various types and intensities of exercise in reducing blood pressure in hypertensive patients. Additional investigations into types and timing of monitoring methodologies for more rigorously structured exercise programs and for measured outcomes are critical to the study of exercise and its influence on disease prevention and treatment.

■ COMMENTARY

Additional evidence supports the contribution that exercise makes to living a healthy life, in this study, by decreasing SBP.[2-4] A blood pressure reading of 120-129/> 80 mmHg now is considered elevated, and clinical guidelines recommend nonpharmacological lifestyle interventions, including exercise.[1] A sedentary lifestyle, in and of itself, is a risk for cardiovascular disease, and exercise has demonstrated broad benefits for cardiovascular health.[5]

However, the benefits of exercise do not just stop at the heart. Exercise is important for the growth and development of children, reducing the incidence and impact of diseases such as diabetes and cancer, improving mental health, and lowering the risk of falls and their related injuries in older populations.[4]

The challenge is how to help and influence patients to initiate and maintain a regular beneficial exercise regimen. Fewer than 30% of people adhere to current exercise recommendations, and the numbers are even worse for women and adolescents (19% and 20%, respectively). This fact is costing people their lives, an estimated 10% early mortality, and more than an estimated $110 billion in healthcare expenditures.[4] Adhering to recommendations of moderate-intensity exercise for 150 minutes per week with additional muscle-strengthening exercises two days a week is critical to reversing these trends.[4]

Physicians are encouraged to play a role in counseling patients to exercise more often. There is some evidence that this support translates into a more active lifestyle for many.[4,6] Training medical students and encouraging practicing physicians to promote exercise consistently as an evidence-based intervention may help move us closer to a tipping point in terms of patient adherence to exercise recommendations.[6]

When exercise interventions are added to other nonpharmacological interventions, such as weight loss, an evidence-based heart-healthy DASH diet, and reductions in sodium intake, even larger reductions in SBP are observed.[1] Naci et al are to be applauded for their contribution to this end. ■

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ABSTRACT & COMMENTARY

Medication Errors When Patients Transition Out of ICU

By Drayton Hammond, PharmD, MBA, BCPS, BCCCP

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

SYNOPSIS: Three factors associated with decreased odds of an error occurring were daily patient care rounds in the ICU, discontinuing and rewriting medication orders during the transition of care from the ICU to a non-ICU setting, and 16-20 ICU beds in the transferring ICU.

SOURCE: Tully AP, Hammond DA, Li C, et al. Evaluation of medication errors at the transition of care from an ICU to non-ICU location. *Crit Care Med* 2019;47:543-549.

Medication errors may occur at any point during a patient's hospitalization, although transition points from different levels of care (e.g., ED to ICU, ICU to floor, and floor to outpatient setting) add an additional element of potentiating the error until the patient's next formal interaction with a healthcare provider.[1,2] The financial costs and mortality attributable to these errors in the United States represent at least $19.5 billion and 98,000 deaths, respectively.[3] Guidelines and best practice statements for transition of care (TOC) focus predominately on hospital discharge, which has many similarities but also differences compared to an inpatient TOC.[4,5] The extent to which medication errors occur during the TOC from the ICU to a lower acuity inpatient setting and risk factors associated with development or prevention of those errors has not been described.

Tully et al completed a multicenter, observational, seven-day study of patients' first transfer from an ICU to a non-ICU setting within the same institution to describe the point prevalence and types of medication errors and patient-, medication-, and system-specific factors associated with their development.[6] A pharmacist evaluated medication orders that were active within one hour pre- and post-ICU transfer for potential medication errors. These pharmacists were provided training and reference documents to facilitate valid and reliable identification of potential medication errors. Prevalence and characteristics of errors were determined using descriptive statistics. Characteristics between those TOCs with and without a medication error were compared. Characteristics with a P value < 0.05 were considered for inclusion in a multivariate logistic regression analysis to determine independent risk factors for medication errors at TOC.

Of the 985 TOCs evaluated, 450 had at least one medication error. Most patients experienced a single error (55.1%), although the mean number of errors was 1.88 (standard deviation, 1.30; range, 1-9). The most common error types were continuation of a medication with an ICU-specific indication (28.4%), untreated condition (19.4%), and medication without a clear indication (11.9%). The most common untreated conditions were cardiac (27.6%) or neurologic (12.9%) in nature. Three-quarters of errors reached patients, although 94.2% did not cause patient harm. For those errors that did cause patient harm, the most common types of errors were incorrect dose (22.6%) and untreated condition (18.9%), and medication classes were anti-infective (28.6%), cardiovascular (18.4%), and neurologic (12.2%). Patient-specific factors associated with increased odds of medication errors were renal replacement therapy during ICU stay (odds ratio [OR], 2.93; 95% confidence interval [CI], 1.42-6.05) and number of medications ordered following TOC (OR, 1.08; 95% CI, 1.02-1.14). Medication-specific factors associated with increased odds of medication errors were receipt in the ICU of an anti-infective agent (OR, 1.66; 95% CI, 1.19-2.32), hematologic agent (OR, 1.75; 95% CI, 1.17-2.62), and intravenous fluid, electrolyte, or diuretic agent (OR, 1.73; 95% CI, 1.21-2.48). System-specific factors associated with increased odds of medication errors were community teaching hospital (OR, 3.96; 95% CI, 1.79-8.79) and 500-999 total inpatient hospital beds (OR, 4.26; 95% CI, 1.05-17.32). System-specific factors associated with lower odds of medication errors were daily patient care rounds in the ICU (OR, 0.15; 95% CI, 0.007-0.34), discontinuing and rewriting medication orders during the TOC from the ICU to a non-ICU setting (OR, 0.36; 95% CI, 0.17-0.73), and 16-20 ICU beds in the transferring ICU (OR, 0.40; 95% CI, 0.21-0.74).

■ COMMENTARY

Medication errors occur in almost 50% of patients transitioning from the ICU to a non-ICU setting. While all errors placed patients at an increased risk for harm, approximately 5% resulted in patient harm during the hospitalization. The quantity and extent of harm from these errors likely are underestimated for at least three reasons. First, errors that were recognized and resolved during order verification likely were underreported because the data collection process was more complex for

capturing and recording these types of errors. Additionally, the duration errors persisted, including presence of the error at hospital discharge, was not evaluated. Because of the retrospective nature of this research, interventions to resolve these errors were unable to be provided after they were identified. Finally, there was at least one dedicated pharmacist for each ICU from which patients were transferred. Pharmacists frequently recognize and resolve minor and major medication errors.[7,8] However, approximately one-third of ICUs in the United States do not employ a partially or fully dedicated pharmacist.[9] The quantity and harm from medication errors at institutions without dedicated ICU pharmacist services likely is greater than reported in this research.[7]

The three factors associated with lower odds of an error were system- and process-focused in nature and represent opportunities for improving patient safety while also likely improving other financial and patient care metrics.[10] While implementing or improving the structure and formality of direct patient care rounds is a significant undertaking, the benefits can be substantial.[10] Similarly, reducing the size of the critical care service to accommodate 16-20 patients at most may require additional resources but likely will increase the ability of all members of the healthcare team to adequately provide care for these patients. The final factor (discontinuing and rewriting medication orders during TOC) is straightforward to implement in most electronic health records and TOC workflow processes.[11]

The research by Tully et al may serve as both a call to action for institutions that are at an increased risk for medication errors and a trove of hypothesis-generating data for investigators interested in improving patient safety through process changes. ■

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ABSTRACT & COMMENTARY

EEG Reactivity for Prediction of Neurological Outcomes After Cardiac Arrest

By Peter B. Forgacs, MD

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

SYNOPSIS: Researchers found that EEG-R testing, by itself, is not sufficiently reliable to predict neurological outcomes after cardiac arrest.

SOURCE: Admiraal MM, van Rootselaar AF, Homeijer J, et al. EEG reactivity as predictor of neurological outcome in postanoxic coma: A multicenter prospective cohort study. *Ann Neurol* 2019; May 24. doi: 10.1002/ana.25507. [Epub ahead of print].

Neurological prognostication in patients who regain consciousness immediately after cardiac arrest remains challenging. Current standard clinical practice guidelines recommend a multimodal approach in assessment of neurological prognosis after cardiac arrest, including bedside examination (i.e., presence of brainstem reflexes), evidence of cortical (N20) response on somatosensory-evoked potential (SSEP) examination,

laboratory markers of neuronal injury (i.e., levels of neuron specific enolase [NSE]), and imaging evidence (CT and/or MRI) of overwhelming neuronal injury. In addition, the value of many electroencephalographic (EEG) features increasingly is explored in assessment of comatose postcardiac arrest patients, particularly since continuous EEG monitoring became standard of care as part of various targeted temperature management (TTM) protocols. Among these features, lack of EEG-R is considered one such important indicator for poor outcome. In fact, all major U.S. and European guidelines include EEG-R as a prognostic marker after cardiac arrest.

However, none of these guidelines, including the American Clinical Neurophysiology Society (ACNS) Standardized Critical Care EEG Terminology, provide specific descriptions of stimulus administration during testing or precise definitions for determining presence or absence of EEG-R. Furthermore, most studies assessing the relationship of EEG-R and clinical outcomes either have been relatively small or designed retrospectively with variable results. Consequently, the value of EEG-R in neurological prognostication after cardiac arrest remains unclear.

In this large, multicenter, prospective cohort study, Admiraal et al used a rigorous standardized protocol for testing of EEG-R. A total of 160 patients were enrolled in three Dutch hospitals, and EEG-R was assessed twice daily while patients underwent continuous EEG monitoring. The protocol for EEG-R testing included a fixed set of auditory, visual, tactile, and noxious stimuli employed three times in a row at each evaluation. Three experienced EEG readers blinded to all clinical variables and patient outcomes independently assessed EEG-R, defined as a change in EEG amplitude or frequency at least twice in response to any of the stimuli. Increased muscle activity or stimulus-induced rhythmic or periodic discharges (SIRPIDS) were not considered as EEG-R. If the raters disagreed, a majority vote was used to decide the presence of EEG-R.

As a secondary analysis, EEG-R also was re-evaluated in a consensus meeting in cases without unanimous decision. Thresholds for accurate prediction of good or poor outcomes were predefined based on the presence or absence of EEG-R, respectively, both using EEG-R alone or added to a multimodal prediction algorithm. Multimodal assessments included brainstem reflexes, N20 response of SSEP at 72 hours, and graded EEG categories based on background abnormalities in addition to EEG-R.

The main findings of the study showed that the absence of EEG-R predicted poor outcome with a specificity of 82% (below the predefined > 95%) and a sensitivity of 73%, while the presence of EEG-R predicted good outcome with a specificity of 73% (below the predefined > 80%) and a sensitivity of 82%. When EEG-R was added to a multimodal model, specificity of poor outcome prediction increased only marginally (from 98% to 99%), and specificity of good outcome prediction increased moderately (from 70% to 89%).

Notably, while inter-rater reliability was relatively good, there was poor agreement between the majority vote vs. the consensus meeting (ICC of 0.40). Thus, the authors concluded that EEG-R testing alone is not sufficiently reliable for neurological outcome prediction after cardiac arrest. In addition, EEG-R adds no substantial value to multimodal assessments for poor outcome prediction, but it may add value to the prediction of good outcomes.

■ COMMENTARY

This was the first, prospectively designed, large, multicenter study assessing the value of EEG-R in neurological prognostication after cardiac arrest. Even though EEG-R is recommended by practice guidelines as an appropriate indicator for outcomes in patients who remain comatose after severe anoxic brain injury, there have been no previous studies of this scale assessing its prognostic value using a standardized, prospectively designed protocol. The results of this study suggest that even using a carefully executed protocol with a systematic approach, EEG-R is not sufficiently reliable to predict neurological outcomes in post-cardiac arrest patients.

Major efforts are devoted to find early but accurate tools for assessing neurological recovery after cardiac arrest. Recent advancements in acute medical care and novel therapeutic interventions, such as various targeted temperature protocols (including therapeutic hypothermia), have led to improved survival and better neurological outcomes after severe anoxic brain injuries. Nevertheless, in current clinical practice, withdrawal of life-sustaining therapy (WLST) decisions continue to drive mortality in patients who do not regain consciousness readily after cardiac arrest.

Therefore, the results of most studies assessing prognosis carry the risk that self-fulfilling prophecies may affect the outcomes and limit the interpretation of results. While the ratio of WLST was relatively low and EEG-R findings were not used in clinical decision-making, the results should be interpreted with caution.

This study underscores the immense continued need for additional studies to develop highly precise and reproducible clinical or diagnostic assessments for accurate early neurological prognostication of comatose post-cardiac arrest patients. ■

PHARMACOLOGY UPDATE

Glucagon Nasal Powder (Baqsimi)

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

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

The FDA has approved a noninjectable, needle-free glucagon for the treatment of severe hypoglycemia. Baqsimi is an intranasal device that delivers glucagon powder.

INDICATIONS

Glucagon nasal powder (GNP) is indicated for the treatment of severe hypoglycemia in patients (≥ 4 years of age) with diabetes.[1]

DOSAGE

The recommended dose is 3 mg (one actuation of the intranasal device) into one nostril.[1] GNP is available as an intranasal device containing a single dose of 3 mg of glucagon.

POTENTIAL ADVANTAGES

This formulation provides a more convenient administration of glucagon compared to the current emergency kit that requires mixing and injection. GNP is easier to administer with fewer failures for nonmedically trained individuals.[2] The frequency of nausea may be lower with intranasal vs. intramuscular administration.

POTENTIAL DISADVANTAGES

Most frequent (> 30%) adverse reactions are watery eyes, nasal congestion, nasal itching, and runny nose.[1] When administered by trained healthcare professionals in a nonemergency setting, there is a slight delay in glycemic response as symptoms of hypoglycemia were greater in the intranasal group for the first 45 minutes.[3] Glucose concentration lagged in the intramuscular group administration by about five minutes.

COMMENTS

The efficacy of intranasal vs. intramuscular glucagon was evaluated in three studies. The first study was a randomized, open-label, crossover study of adults with type 1 diabetes (n = 66), the second study included both type 1 and type 2 diabetic adults (n = 80), and the third study was conducted with pediatric type 1 diabetes subjects (age 4 years up to < 17 years of age; n = 48).[1,3,4]

In both adult studies, hypoglycemia was induced by insulin, to < 60 mg/dL in the first study and < 50 mg/dL in the second study. Subjects were randomized to 3 mg of intranasal glucagon or 1 mg of intramuscular glucagon and then crossed over to the other treatment one to four weeks apart. Treatment success was defined as either an increase in blood glucose to ≥ 70 mg/dL or an increase of ≥ 20 mg/dL from glucose nadir within 30 minutes after administration. Treatment success was 100% for both formulations in study 1 and 98.8% for intranasal glucagon and 100% for intramuscular glucagon in study 2.

In the pediatric study, subjects received either 2 mg or 3 mg of intranasal glucagon or a dose of weight-based (0.5 mg or 1 mg) intramuscular glucagon. All subjects who received intramuscular glucagon (24/24) or 3 mg of intranasal glucagon (36/36) achieved a blood glucose level ≥ 20 mg/dL within 30 minutes.[4] Mean times to achieving glucose ≥ 20 mg/dL ranged from 10.8 minutes to 14.2 minutes.[1] Nausea, with or without vomiting, tended to be less frequent with intranasal vs. intramuscular glucagon.

In two real-world studies, one that included adults and one that included a pediatric population, intranasal glucagon was effective, generally well tolerated, and easy to use.[5,6] In a simulation study (administered to manikin), > 90% of instructed caregivers delivered the full dose of intranasal glucagon vs. 13% for intramuscular glucagon.[2] Common cold and concomitant use of nasal decongestant do not significantly alter the effect of intranasal glucagon.[7] The cost for both formulations is the same ($280.80 per unit).

CLINICAL IMPLICATIONS

The American Diabetes Association recommends glucose intake to treat hypoglycemia (e.g., 15 g of glucose and check in 15 minutes).[8] For severe hypoglycemia (too long to treat with glucose), glucagon injection is recommended. This requires reconstitution and administration by injection. Intranasal glucagon offers the first glucagon formulation for emergency treatment that can be administered without an injection. It appears to be an easier-to-use, needle-free, equally effective alternative to injectable glucagon. ■

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CME QUESTIONS

1. **Which food item is more likely to prevent type 2 diabetes?**
   a. Grass fed beef
   b. Lean pork
   c. Salmon
   d. Spinach

2. **Which exercise intervention resulted in the largest decreases in mean systolic blood pressure among patients with hypertension?**
   a. Endurance
   b. Isometric resistance
   c. Dynamic resistance
   d. Combination

3. **In the study by Tully et al, which factor was associated with lower odds of a medication error occurring during transition of care (TOC)?**
   a. A total of 500-999 inpatient hospital beds
   b. Community teaching hospital
   c. Discontinuing and rewriting medication orders during the TOC from the ICU to a non-ICU setting
   d. Number of medications ordered following TOC

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.