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ABSTRACT & COMMENTARY

Statins Associated with Lower Parkinson's Risk in Diabetics

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Dr. Henchcliffe reports she is on the speakers bureau and advisory boards for Teva, IMPAX, and ACADIA; is on the advisory board for U.S. World Meds; and is a consultant for Cynapsus and Pfizer.

SYNOPSIS: In approximately 50,000 individuals with Parkinson's disease and diabetes, identified from a National Health Insurance database in Taiwan, statin use was dose-dependently associated with lower risk of Parkinson's disease. This strengthens the argument for a possible protective role for statins.

SOURCE: Lin KD, Yang CY, Lee MY, et al. Statin therapy prevents the onset of Parkinson's disease in patients with diabetes. *Ann Neurol* 2016;80:532-540.

Recent studies have highlighted the importance of attention to overall patient health in Parkinson's disease (PD). In particular, there is concern that modifiable cardiovascular risk factors may play a role in risk of PD. In this study, Lin et al randomly sampled 1 million patients from a reimbursement database of the National Health Insurance (NHI) program in Taiwan. ICD-9 codes were used to identify patients with diabetes, and inclusion in this group required at least three visits within a 30-day to one-year period. ICD-9 codes for PD and secondary parkinsonism, as well as anti-PD medication use, were used to define those with PD for the purposes of this study. Those presenting with dementia or malignancy before the index date (first visit for diabetes) were excluded. Statin dose and duration was determined, and statin users were compared with patients not taking statins. Of patients included in the study, average age was 59 ± 11 years, 48% were women, 76% had hypertension, 69% had hyperlipidemia, 39% had ischemic heart disease, and 28% had suffered a stroke. The crude hazard ratio of PD incidence of statin users vs. non-users was 0.60 (95% confidence interval

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[CI], 0.51-0.69) in men and 0.65 (95% CI, 0.57-0.74) in women. Relative risk (RR) was 0.70 (95% CI, 0.63-0.79). A Cox regression analysis demonstrated a significant trend for dose-dependence of this effect. However, when statins were examined individually, lovastatin did not seem to associate with lower risk of PD, in contrast to simvastatin, atorvastatin, and "other" (pravastatin plus fluvastatin). The incidence of PD was higher with increasing age, as expected, and also higher in patients with strokes, but lower in patients with hyperlipidemia. Of note, regardless of statin use, incidence of PD was actually higher in women than men in this study of individuals with diabetes, as seen previously in diabetics, but contrary to the usual male preponderance of this disorder.

■ COMMENTARY

Although multiple previous studies have attempted to pin down the relationship of statin use and PD, the true nature of the association has proved elusive. Statin prescription targets lowering low-density lipoprotein cholesterol, as a competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase. However, statins also may inhibit neuroinflammatory processes and reduce microglial activation, increase antioxidant pathways, and there is good evidence that they provide neuroprotection in animal models of disease as well as in cells in tissue culture. This study very comprehensively analyzed the association of statin use with PD incidence, specifically in individuals with diabetes. Using multiple regression analyses, the authors found that even after adjusting for a number of factors (including age, hypertension, hyperlipidemia, stroke, ischemic heart disease, Charlson comorbidity index), there was a "protective effect" against PD. A strength of the study is that this effect was dose-dependent. The NHI covers 98% of the Taiwanese population as of 2005 (although the study goes back to 2001), and the large number of patients included, the long-term follow-up data available, and finding of a dose relationship make this study highly compelling. Nonetheless, inherently it is a study of association, and not causation, and the article title states that statin therapy prevents PD in those with diabetes and, therefore, should not be misinterpreted. As the authors stated, more studies will be needed and an interventional study would provide critical data in this regard. The use of ICD-9 codes without the ability to verify diagnosis limits the study's strength somewhat. But more importantly, the use of ICD-9 codes for secondary parkinsonism, in addition to PD, raises many questions about what is under examination precisely. This raises questions as to the mechanisms underlying the association described in this study. Finally, the study strongly suggests a pragmatic approach to curbing the effect of neurodegenerative disorders, including PD, in the near future, and it certainly emphasizes the importance of attention to general health issues in healthy aging. ■

[The study strongly suggests a pragmatic approach to curbing the effect of neurodegenerative disorders, including Parkinson's disease, in the near future, and it certainly emphasizes the importance of attention to general health issues in healthy aging.]

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ABSTRACT & COMMENTARY

Changing Gut Microbiota to Prevent Type 2 Diabetes

By Atreyi Mukherji, MD, MPH, FRCPC

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

SYNOPSIS: The long-term consumption of a healthy diet, such as the Mediterranean diet or low-fat/high complex carbohydrate diets, may exert a protective effect on the development of type 2 diabetes by changing the gut microbiota, increasing the abundance of *Roseburia* genera and *Faecalibacterium prausnitzii*, respectively.

SOURCE: Haro C, Montes-Borrego M, Rangel-Zuniga OA, et al. Two healthy diets modulate gut microbial community improving insulin sensitivity in a human obese population. *J Clin Endocrinol Metab* 2016;101:233-242.

Obesity is a chronic disease and its pathophysiology has been linked to changes in the gut microbiota.[1] Gut microbiota are a complex and diverse ecosystem of microorganisms in the human colon that act collectively as a fully integrated organ. Gut microbiota are involved in extracting nutrients, regulating innate and adaptive immunity, and helping control energy balance.[2] Animal model studies show that obesity is associated with an increase in the *Firmicutes*/*Bacteroides* bacteria ratio.[1] In addition, the intestinal absorption of bacterial components, such as endotoxin lipopolysaccharides, bacterial DNA, and flagellins, activate Toll-like receptors that favor insulin resistance.[3] A few studies show changes in gut microbiota by dietary intervention.[4,5] The Western diet increases endotoxemia, suggesting a disruption in the intestinal barrier and an increase in gram-negative bacteria content in the microbiota.[4,6] A high-fat, high-carbohydrate diet induces endotoxemia and inflammation,[4,7] whereas a high-fruit and high-fiber meal or intake of a polyphenol preparation, such as resveratrol, does not induce such changes.[8,9]

The objective of the Haro et al trial was to study the changes in gut microbiota after one year of consumption of two healthy diets: the Mediterranean diet (MedDiet) or the low-fat, high complex carbohydrate (LFHCC) diet in 20 obese patients with coronary heart disease (CHD). The study was conducted in a subgroup of the CORDIOPREV study, an ongoing prospective, randomized, open, controlled trial in patients with stable CHD (event-free for six months prior to enrollment). Patients ranged from 20-74 years of age and were excluded if they had severe CHD with life expectancy of < 5 years. All patients were on standardized treatments for CHD. The MedDiet composition was 35% fat with 22% monounsaturated fat and the LFHCC diet contained 28% fat with 12% monounsaturated fat. To ensure consistency of diet, all patients in the MedDiet group were provided olive oil. Food packs, including low-fat foods (cereal, biscuits, pasta) of similar costs, were provided to patients in the low-fat group. Plasma and fecal samples were analyzed using various molecular technologies to assess change in microbiota and metabolomic analysis.

The main findings of the study were changes in microbiota. The LFHCC diet increased *Prevotella* genera and decreased the *Roseburia* genera, whereas the MedDiet decreased the *Prevotella* and increased the *Roseburia* and *Oscillospira* genera ($P = 0.028$, 0.002, and 0.016, respectively). *Parabacteroides distasonis* ($P = 0.025$) and *Faecalibacterium prausnitzii* ($P = 0.020$) were more abundant after consumption of the MedDiet and LFHCC diet, respectively. The increase in *Roseburia* in the MedDiet group and the increase in *F. prausnitzii* in the LFHCC diet group also were accompanied by an increase in insulin sensitivity index for both diets ($P = 0.019$ and $P = 0.005$, respectively) when measured by oral glucose tolerance test performed at baseline and after one year of dietary intervention. The main metabolic changes noted in the fecal analysis were the profiles of the amino acids, peptides, and sphingolipid metabolism, which could be linked to changes in the gut microbiota.

■ COMMENTARY

This preliminary study showed that long-term (one-year) consumption of two heathy diets (MedDiet and LFHCC diet) was associated with changes in gut microbiota population in the colon, as well as changes in some aspects of the metabolic profile. An improvement in insulin sensitivity also was observed, as measured by the glucose tolerance test in the LHFCC diet, suggesting that these diet patterns may have a protective effect on development of type 2 diabetes.

Roseburia genera and *F. prausnitzii* are butyrate-producing bacteria that are found to be low in

patients with type 2 diabetes. *Roseburia* could play an important role in gut health[10] and is known to produce an anti-inflammatory effect on the gut.[10-12] An antimicrobial effect through inhibiting *Bacillus subtilus* in the colon is another mechanism by which *Roseburia* genera have been shown to affect the gut microbial population in the colon.[13] *F. prausnitzii,* along with other butyrate-producing bacteria, previously have been shown to increase in people with metabolic syndrome on the MedDiet, but not the LF-HCC diet.[14] The increase in *Prevotella* in the LFHCC diet is thought to be an adaptation of the microbiota to enhance extraction of calories from carbohydrates that escape digestion in the small intestine and are fermented in the gut.[15] This also is born out in a study demonstrating *Prevotella* abundance with long-term diets rich in carbohydrates.[16]

In conclusion, the observations in this study are provocative and suggest the development of a new hypothesis about how changes in the existing gut microbiota may be one mechanism by which dietary interventions could be a therapeutic tool for chronic disease. Further studies are required to assess the effect of these findings in clinical practice. Perhaps a potential exists for a more customized (personalized) approach to the implementation of dietary interventions based on the disease and the individual patient. In the interim, clinicians should continue to utilize evidence-based dietary interventions such as the MedDiet for chronic disease, including cardiovascular disease and breast cancer. ■

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ABSTRACT & COMMENTARY

Warning: Reactivation of Hepatitis B Virus Coinfection During Treatment of Chronic Hepatitis C Virus Infection

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

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

SYNOPSIS: Prior to initiation of hepatitis C virus treatment with direct-acting antivirals, patients should be screened for hepatitis B virus coinfection. Those who are hepatitis B virus-infected should receive ongoing monitoring for flares and reactivation of hepatitis B.

SOURCE: FDA Drug Safety Communication. FDA warns about the risk of hepatitis B reactivating in some patients treated with direct-acting antivirals for hepatitis C. Available at: http://bit.ly/2fAYUak. Accessed Oct. 17, 2016.

The FDA identified a total of 24 cases of confirmed reactivation of hepatitis B virus (HBV) coinfection during treatment of hepatitis C virus (HCV) infection with direct-acting antivirals (DAA). The patients' HCV genotypes were heterogeneous. Reactivation of HBV occurred a mean of 52 days after initiation of treatment of HCV infection, with most cases occurring within four to eight weeks. Two patients died as a consequence, while another required liver transplantation. The characteristics of the HBV coinfection prior to reactivation were variable: Seven had detectable HBV DNA, four were HBsAg positive but DNA negative, three were negative for both, and the results were unknown for the remaining 10.

After HBV reactivation, at least 12 of the 24 received treatment with either tenofovir or entecavir, and at least six received no treatment. Anti-HBV treatment was delayed in at least five of the 12, and one of these patients died; it was possibly delayed in at least three others, including the patient who required transplantation. DAA therapy was discontinued in eight patients when transaminase elevation was recognized. Overall, the FDA described the following as the commonly encountered sequence: " ... initiation of DAA-based HCV treatment, rapid drop of HCV RNA to undetectable levels within one to two weeks after normalization of transaminase levels (if they were elevated), followed by a rise in HBV DNA with or without increase in transaminases between weeks four to eight."

As a consequence of these observations, the FDA now requires that a boxed warning be added to the drug labels of the currently approved DAAs. This warning directs healthcare providers to screen and monitor for flare-ups and reactivation of HBV coinfection in patients receiving these drugs. Screening should include testing for both HBsAg and anti-HBc, with quantitation of plasma HBV DNA prior to initiation of DAA in those with serological evidence of infection. In those with HBV coinfection, in addition to clinical evaluation, monitoring should include serial measurement of HBsAg, HBV DNA, transaminase levels, and bilirubin, both during and after treatment of HCV infection.

■ COMMENTARY

The fact that this adverse event was not observed during the clinical trials required for FDA approval has a simple explanation: Coinfection with HBV excluded patients from participation. Flares had been observed during treatment with regimens that included interferon-alpha, but this is confounded by the complexity of the effects of the latter, which has both antiviral and immunomodulatory activities.

The mechanistic explanation for these flares and reactivations during receipt of DAA therapy is not known. It is of interest that plasma levels of HCV generally exceed those of HBV in coinfected patients, suggesting the possibility of an undefined interaction between the two. One reasonable potential explanation for the occurrence of reactivation and flares is that prevention of HCV replication may alter the local hepatic milieu such that local nonspecific immune activity is increased, leading to hepatic damage in the presence of HBV coinfection.[1] ■

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PHARMACOLOGY UPDATE

Eteplirsen Injection (Exondys 51)

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

Dr. Elliott is Medical Director, Pharmacy, Northern California Kaiser Permanente, and Assistant Clinical Professor of Medicine, University of California, San Francisco. Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

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

The FDA has approved the first drug to treat patients with Duchenne muscular dystrophy (DMD). Eteplirsen, an antisense oligonucleotide, was granted fast-track and orphan designations and was approved under the accelerated approval pathway.[1] This pathway provides earlier patient access while the sponsor conducts a clinical trial to confirm anticipated clinical benefit. Eteplirsen is marketed as Exondys 51.

INDICATIONS

Eteplirsen is indicated for the treatment of DMD in patients who present with confirmed mutation of the DMD gene that is amenable to exon 51 skipping.[2]

DOSAGE

The recommended dose is 30 mg/kg once weekly.[2] Eteplirsen is available as 100 mg (2 mL) and 500 mg (10 mL) single-dose vials.

POTENTIAL ADVANTAGES

Eteplirsen is the first FDA-approved drug for DMD.

POTENTIAL DISADVANTAGES

The clinical benefit of eteplirsen has not been established. The most frequent adverse events were balance disorder (38%), vomiting (38%), and contact dermatitis (25%).[2]

[The sponsor currently is recruiting for a 48-week confirmatory study with the six-minute walk test as the primary endpoint and percent of dystrophin positive fibers and maximum inspiratory/expiratory pressure percent predicted as secondary endpoints.]

COMMENTS

DMD is caused by deletion in the dystrophin mRNA reading frame, leading to lack of expression of dystrophin protein, important in keeping the muscle cell intact. Eteplirsen is a 30-nucleotide-long phosphorodiamidate morpholino oligomer that induces skipping of exon 51 in DMD pre-mRNA by selectively binding to the exon of dystrophin pre-mRNA, restoring the open reading frame. This results in expression of a less functional (truncated) dystrophin. Eteplirsen was evaluated in three clinical studies in patients with confirmed mutation of the DMD gene that was amenable to exon 51 skipping. Study one randomized 12 subjects (four each) to eteplirsen 30 mg/kg, 50 mg/kg, or placebo for 24 weeks. The primary endpoint was an increase in dystrophin production and the six-minute walk test. After 24 weeks, there were no significant differences in placebo or either treatment arm. Study two included all 12 subjects from study one and continued for an additional four years. Four subjects previously on placebo in study one were randomized to 30 mg/kg or 50 mg/kg in study two. The primary endpoint was the six-minute walk test. No significant difference was demonstrated between treated subjects compared to an external control. Improvement in dystrophin levels was difficult to assess due to insufficient baseline levels (muscle biopsy) from study one. In study three, 12 subjects with baseline muscle biopsies were treated for 48 weeks at 30 mg/kg. The pre-treatment level of dystrophin was 0.16% ± 0.12% of that in a healthy subject compared to 0.44% ± 0.43% after treatment. Only one subject experienced an increase > 1% of that in a healthy subject. This represented a statistically significant increase of 0.28% but is not thought to be clinically meaningful. It is believed that 10% is needed to be a clinically meaningful level.[3]

CLINICAL IMPLICATIONS

DMD is an X-linked recessive neuromuscular disorder, resulting in the absence or near-absence of dystrophin protein in the muscle cells. This leads to muscle damage, loss of physical function, and ultimately premature death due to respiratory and/or cardiac failure. Eteplirsen has been shown to marginally improve dystrophin levels, albeit as a less functional version, but only in those patients with a mutation amenable to exon 51 skipping (approximately 13% of all DMD patients). Clinical benefit has not been demonstrated. There was much debate whether there was sufficient efficacy evidence to support FDA approval based on dystrophin levels. In addition, there were concerns about flaws in the sponsor's program, including poor quality of many of the biopsies.[3] The results of study two were published, but after further FDA review, the improvement in dystrophin levels were considered to be "greatly overstated."[3,4] The FDA advisory committee voted against approval; however, the FDA appeared to acquiesce to public pressure and granted an accelerated approval. The sponsor currently is recruiting for a 48-week confirmatory study with the six-minute walk test as the primary endpoint and percent of dystrophin positive fibers and maximum inspiratory/expiratory pressure percent predicted as secondary endpoints.[5] The cost for eteplirsen is $480 per 30 mg. This translates to $15,840 per week for a 33 kg patients and $24,000 per week for a 50 kg patient, or $823,680-$1,248,000 per year. ■

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Clinical Briefs

By Louis Kuritzky, MD

The Importance of Low Uric Acid in Gout Patients

SOURCE: Ruoff G, Edwards NL. Overview of serum uric acid treatment targets in gout: Why less than 6 mg/dL? *Postgrad Med* 2016;128:706-715.

In addition to the burden caused by painful acute gout flares, inadequately managed gout can lead to substantial long-term disability and deformity. Not everyone presenting with hyperuricemia develops gout or requires treatment. Indeed, ≤ 10% of patients demonstrating marked elevation in serum uric acid (> 9.0 mg/dL) go on to develop gout annually. Once patients experience diathesis to deposit inflammatory urate crystals in joints (or other tissues) during a single attack of gout, ≥ 90% will suffer another attack within 10 years, suggesting that most sufferers will not be so lucky as to experience a one-time event.

In vitro, crystals tend to form when uric acid levels exceed about 6.8 mg/dL, reflecting saturation at that point. Various guidelines suggest clinicians treating gout should aim for a lowering to a minimum of 6.0 mg/dL, noting that sustained uric acid lowering ultimately is associated with a disappearance of flares as well as a dissolution of tissue deposits of uric acid (e.g., tophi). Indeed, the rate of tophus dissolution has been shown to be proportional to the degree of lowering of serum uric acid levels.

Although clinicians might be tempted to aim for a goal just below 6.8 mg/dL, it is probably unwise to do so. Dietary and physiologic changes may cause fluctuation substantially above 6.8 mg/dL unless a wide margin of safety is created. Tissue deposition of uric acid can cause chronic silent joint destruction at elevated levels of uric acid. Consistent abolition of acute flares has been confirmed only when uric acid levels < 6.0 mg/dL are maintained over the long term. ■

Gabapentin and Pregabalin Effective for Refractory Chronic Pruritus

SOURCE: Matsuda K, Sharma D, Schonfeld AR, Kwatra SG. Gabapentin and pregabalin for the treatment of chronic pruritus. *J Am Acad Dermatol* 2016;75:619-625.

Clinicians usually are successful when they treat pruritus with antihistamines. Some categories of pruritus prove somewhat refractory to intervention, such as uremic pruritus and neurogenic pruritus. When traditional antihistamines (e.g., diphenhydramine, hydroxyzine, cetirizine, loratadine) have failed, what else might work?

Gabapentin and pregabalin are analogues of gamma-aminobutyric acid, but do not actually interact with gamma-aminobutyric acid receptors. They generally are well tolerated, and although originally investigated for their antiepileptic potential, the authors addressed 37 different randomized, controlled trials of gabapentin, pregabalin, or the combination in a variety of different itch syndromes. Gabapentin and pregabalin were demonstrated to produce substantial clinical success in syndromes as far ranging as uremic pruritus, notalgia paresthetica, post-spinal cord pruritus, and cancer chemotherapy-related pruritus.

The tolerability of gabapentin and pregabalin was reflected in the modest discontinuation rates due to adverse effects (6-8%). Although most of the trials were small and lacked long-term follow-up, the promising results support consideration of gabapentin, pregabalin, or both for patients presenting with refractory pruritus. ■

Does Technology Accelerate Weight Loss?

SOURCE: Jakicic JM, Davis KK, Rogers RJ, et al. Effect of wearable technology combined with a lifestyle intervention on long-term weight loss: The IDEA randomized clinical trial. *JAMA* 2016;316:1161-1171.

For most patients, long-term weight loss is modest, whether they use diet, exercise, pharmacotherapy, or a combination. Only bariatric surgical interventions provide consistent and sustained substantial weight loss (> 20%) for the majority of patients. In this age of technological advances, will sophisticated tools lead our patients to enhanced weight loss?

Jakicic et al enrolled overweight and obese adults (n = 471) in a randomized trial comparing traditional interventions, such as education about diet, exercise, and counseling, with traditional interventions plus gadgetry, which included wearable devices to monitor physical activity and a web-based interface to monitor diet and activity. The authors analyzed the effect of the added gadgetry at 24 months.

Although both groups enjoyed weight loss at the conclusion of the 24-month intervention, the group randomized to add-on gadgetry actually experienced *less* weight loss than the group that simply received traditional diet and exercise advice (3.6% vs. 6.2%). Previous shorter-term studies have been more supportive of wearable devices, but perhaps the gloss wears off in longer-term studies such as this one. ■

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CME QUESTIONS

1. A population-based study of approximately 50,000 patients with diabetes and Parkinson's disease (PD) found that:

a. more men than women with diabetes developed PD.

b. in individuals with diabetes, there is little to no age association of PD incidence.

c. lovastatin prevented PD.

d. statin therapy was associated with lower incidence of PD.

2. Which of the following statements is *false* regarding the effect of gut microbiota and chronic disease?

a. Obesity is linked with increase in *Firmicutes/Bacteroides* ratio.

b. The improvement in insulin sensitivity in obese patients found in this study after one year of consumption of a Mediterranean diet or low-fat, high-complex carbohydrate diet is directly attributable to the changes observed in the microbiota.

c. The microbial population in the human colon has been shown to adapt to specific diet compositions.

d. Gut microbiota are involved in extracting nutrients, regulating innate and adaptive immunity, and helping control energy balance.

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]

Is Yoga Effective for Treating Asthma?

Is Anxiety a Risk Factor for Cardiovascular Disease?