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Highlights From the Latest in Diabetes Research

Potential Progress for Statin-Intolerant Patients With Elevated LDL Cholesterol

In the U.S., national data indicate that 71 million adults aged ≥20 years—33.5% of this age-group—have elevated LDL cholesterol. Of these, only 34 million are being treated and 23 million (about 33% of all patients) had their LDL cholesterol at targets defined by the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP III). These data indicate that there is considerable room for improvement in initiating or identifying an effective treatment among people with elevated LDL cholesterol and that treatment goals are not where they should be among individuals who are being actively treated. The obesity epidemic and the aging of the populations in many developing countries may conspire to increase the prevalence of elevated LDL cholesterol in the future, a trend that will require added attention to initiating effective treatment in affected individuals. Given the high prevalence of elevated LDL cholesterol, it is of some concern that 10–20% of patients are unable to tolerate statins, which are currently the most efficacious therapy for reducing LDL cholesterol. The primary reason for statin intolerance in these patients is their impact on muscle pain and weakness. As a result, statins are not an attractive treatment option for a large proportion of the affected patient population, a problem that may increase in tandem with increases in the prevalence of elevated LDL in the population as a whole. The GAUSS trial addressed the need for effective therapies among individuals for whom statins are not a viable option. The trial focused on AMG145, a monoclonal antibody to PCSK9, which is involved in LDL receptor function. The phase 2 study randomized 160 statin-intolerant patients aged 18–75 years at 33 sites. Patients were allocated to one of three AMG145 doses (280 mg, 350 mg, or 420 mg), AMG145 420 mg + 10 mg ezetimibe, or 10 mg ezetimibe + placebo. The primary end point was percent change in LDL cholesterol between baseline and week 12. A number of secondary and exploratory end points were also examined, including absolute change in LDL cholesterol, percent change in HDL cholesterol, and adjudicated clinical cardiovascular events and mortality. The results were striking: LDL cholesterol was reduced 41, 43, and 51% in the AMG145 280 mg, 350 mg, and 420 mg groups, respectively, and 61% among participants who received AMG145 420 mg + 10 mg ezetimibe. In contrast, LDL cholesterol was reduced by only 15% in the 10 mg ezetimibe + placebo group. AMG145 also resulted in modest increases in HDL cholesterol. Sixty and fifty-nine percent of patients receiving AMG145 and 10 mg ezetimibe + placebo reported adverse events. Of the four serious adverse events, all were in the AMG145 group and none were determined to be associated with treatment. Given that the magnitude of AMG145's impact on LDL cholesterol reduction was similar to that commonly observed with statins, the results of the GAUSS trial may offer promise for millions of patients who do not currently have access to a treatment option that permits them to achieve NCEP goals. — *Helaine E. Resnick, PhD, MPH*

■ Sullivan et al. Effect of a monoclonal antibody to PCSK9 on low-density lipoprotein cholesterol levels in statin-intolerant patients: the GAUSS randomized trial. JAMA. 5 November 2012 [Epub ahead of print]

Resveratrol's Preferential Metabolic Impact

Studies of resveratrol, a polyphenol found in the skin of grapes, have demonstrated improvement in metabolic function in rodents with diet-induced obesity as well as in humans with type 2 diabetes, impaired glucose tolerance, or obesity. In these metabolically abnormal populations, resveratrol had a favorable impact on insulin sensitivity, inflammation, and mitochondrial function (both species); plasma lipids, oxidative stress, and life span (rodents); and plasma glucose (humans). In contrast, resveratrol did not improve metabolic function in normal rodents. Moving this line of investigation forward, Yoshino et al. conducted a randomized, double-blind, placebo-controlled trial of resveratrol supplementation in nonobese, postmenopausal women with normal glucose tolerance to determine resveratrol's impact on various metabolic parameters. For 12 weeks, 15 women received 75 mg/day of resveratrol, and 14 women received placebo. Using a two-stage hyperinsulinemic-euglycemic clamp procedure and infusions of a stable, isotopically labeled tracer, the authors determined that resveratrol did not affect insulin action in liver, adipose tissue, or skeletal muscle, nor did it improve plasma lipids. Moreover, gene expression of several key resveratrol targets in skeletal muscle and adipose tissue biopsies did not differ between the treatment and control groups, nor did body composition. In addition, the authors did not detect resveratrol-induced changes in biological pathways associated with mitochondrial function and inflammation in skeletal muscle and adipose tissue, findings that contrasted with previous studies in rodents and obese humans. Analysis of global transcription changes detected resveratrol effects in only two pathways: kinesin complex and ubiquitin ligase complex. The findings from this trial differ markedly from those of three other published studies in metabolically abnormal humans, which reported favorable results associated with resveratrol administration. However, direct comparisons across these studies are difficult due to differences in their designs and protocols. For example, issues such as variation in the number of subjects, resveratrol dose and duration, timing of the tissue biopsy, and the participants' age, BMI, and glucose tolerance may have contributed to the variability in the results. Nonetheless, the authors concluded that resveratrol

supplementation had no impact in normal, postmenopausal women and that it might only benefit those individuals with impaired metabolic profiles. Considering that resveratrol supplement sales in the U.S. reaches $30 million annually, the authors recommended targeted evaluation of resveratrol supplementation in specific populations. — *Eileen M. Resnick, PhD*

- Yoshino et al. Resveratrol supplementation does not improve metabolic function in nonobese women with normal glucose tolerance. Cell Metab 2012;16:658–664

Metabolically Driven Hyperalgesia: A New Mechanism for Neuropathic Pain

Diabetic neuropathy is a common complication of diabetes that affects multiple systems and has a profound impact on quality of life. One of the most troubling symptoms of neuropathy is pain, but the biological mechanism for the development of neuropathic pain is incompletely understood. Nevertheless, elevated glucose may be a possible risk factor. A recent report by Bierhaus et al. has demonstrated a possible link between hyperglycemia and neuropathic pain through the actions of methylglyoxal, a glucose metabolite. Initial experiments determined that methylglyoxal plasma concentration was significantly higher in diabetic patients with pain compared to those without. Next, investigators evaluated the potential effects of increased methylglyoxal concentration on nerve function. Previous studies showed that glyoxylase 1 (GLO1) (the enzyme that metabolizes methylglyoxal) activity is low in peripheral nerves and in the nerves of diabetic mice, potentially enhancing nerve susceptibility to high methylglyoxal levels. Following this line of reasoning, the authors performed GLO1 knockdown studies to assess the functional impact of elevated methylglyoxal concentrations. Nondiabetic GLO1 knockdown mice experienced latency reduction in noxious heat withdrawal, which also was observed in streptozotocin-induced diabetic wild-type mice. Further studies demonstrated that systemic administration of methylglyoxal decreased the heat pain threshold. Together, these studies demonstrated that diabetes, loss of GLO1, and systemic methylglyoxal administration leads to hyperalgesia. Additional studies in mice determined that methylglyoxal's effects on neurons were likely due to post-translational modification of the nociceptor-specific, voltage-gated sodium channel, $Na_v1.8$. Modifications of this sodium channel were enhanced in mice with high methylglyoxal concentration, loss of GLO1 expression, or diabetes, and knockdown of $Na_v1.8$ resulted in loss of methylglyoxal-induced hyperalgesia. Current-clamp recording in dorsal root ganglion neurons led the authors to conclude that methylglyoxal-induced post-translational modifications of $Na_v1.8$ alter its function, resulting in hyperexcitability of sensory neurons and hyperalgesia. The authors propose that methylglyoxal is a key player in metabolically driven hyperalgesia and could be pursued as a new therapeutic target in diabetic neuropathy. — *Eileen M. Resnick, PhD*

- Bierhaus et al. Methylglyoxal modification of $Na_v1.8$ facilitates nociceptive neuron firing and causes hyperalgesia in diabetic neuropathy. Nat Med 2012;18:926–933

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