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Highlights From the Latest in Diabetes Research

Strong Evidence Supporting Benefits of Mediterranean Diet Among People at High Risk of CVD

The increasing occurrence of obesity and diabetes and the aging of populations in many developed countries have generated great interest in identifying behavioral factors that can be modified to reduce the occurrence of cardiovascular disease (CVD). Data from observational cohort studies and, more recently, from small clinical trials have suggested the potential value of a "Mediterranean" diet. Relative to a "typical American diet" the Mediterranean diet favors higher intake of olive oil, fish, fruits, nuts, and cereals and lower levels of red and processed meats and dairy products. New data from a primary prevention trial shed new light on the potential of this dietary pattern to reduce the occurrence of CVD among at-risk individuals. The PREDIMED study randomized 7,447 men and women aged 55–80 years to one of three groups: a Mediterranean diet supplemented with olive oil, a Mediterranean diet supplemented with nuts, or a control diet in which participants were advised to reduce fat intake. Importantly, participants were not instructed to reduce overall energy intake. Inclusion criteria stipulated that participants were free of CVD at baseline and that they have either diabetes or three CVD risk factors including smoking, hypertension, obesity, elevated LDL, or low HDL cholesterol. The main outcome of the trial was the rate of CVD events, defined as a composite of any the following: myocardial infarction, stroke, or death from cardiovascular causes. Adherence to the intervention was assessed by both self-report and biochemical analysis. During a median follow-up of 4.8 years, there were 288 end points. Analysis revealed significant protective effects for both Mediterranean diet groups, relative to controls, and that the magnitude of benefit was similar in the two intervention arms: the adjusted hazard ratios were 0.70 (95% CI 0.54–0.92) for the olive oil group and 0.72 (95% CI 0.54–0.96) for the nut group, relative to controls. Analysis of biomarkers indicated favorable adherence to the diets in both intervention groups. Even among high-risk individuals in a setting where energy intake is unrestricted, these data provide strong evidence supporting the benefit of a Mediterranean diet supplemented with either olive oil or nuts. Results from PREDIMED raise obvious questions about how to best translate these findings into practice. — *Helaine E. Resnick, PhD, MPH*

■ Estruch et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med 2013;368:1279–1290

Potentially Important Role for Sarcolipin in Skeletal Muscle Thermogenesis

Numerous studies have shown that brown fat plays a major role in non-shivering thermogenesis (NST) and that increased brown fat thermogenesis protects against diet-induced obesity and insulin resistance. However, unlike rodents, most humans have relatively low levels of brown fat, suggesting that obesity- and diabetes-related interventions directed at NST may not necessarily be effective. Recent data from Bal et al. demonstrate that skeletal muscle also plays a key role in NST and that sarcolipin, a regulator of sarcoplasmic reticulum calcium cycling, is required for NST in this tissue. In an initial set of experiments in which intrascapular BAT (representing 60% of all BAT) was removed from both sarcolipin knockout and wild-type mice that were housed at 22 ± 1.5°C, no differences in core temperature were observed between the two groups. However, subsequent experiments in which the temperature was reduced to 4°C showed that sarcolipin$^{-/-}$ mice with ablated BAT could not maintain core temperature and died of hypothermia. In contrast, sarcolipin$^{-/-}$ mice with intact BAT survived, but with a somewhat lower core temperature. Wild-type mice whose BAT was ablated were also able to maintain core temperature during a cold challenge. Collectively, these findings suggested that sarcolipin compensated for loss of BAT and that BAT compensated for loss of sarcolipin. Interestingly, this report also showed that loss of sarcolipin resulted in diet-induced obesity in mice, suggesting that it not only mediates NST in skeletal muscle but is also associated with overall energy balance. The authors highlight the potential application of their findings by pointing out that sarcolipin mediates temperature in animals with low brown fat levels, including humans. Further, in humans, sarcolipin levels are several times higher than those observed in rodents, a consideration that may have therapeutic application in the future. — *Helaine E. Resnick, PhD, MPH*

■ Bal et al. Sarcolipin is a newly identified regulator of muscle-based thermogenesis in mammals. Nat Med 2012;18:1575–1579

A New Mechanism for an Old Therapy: Metformin and Glucagon Signaling

Metformin is the most commonly prescribed pharmaceutical for reducing hepatic glucose production for treatment of type 2 diabetes. Metformin and phenformin are members of the biguanide class of therapeutics whose mechanism of action is poorly understood. Based on the observation that glucagon increases hepatic glucose production, a new report by Miller et al. focused on the potential link between biguanide action and glucagon. Glucagon binds to plasma membrane receptors, causing adenylyl cyclase activity, an increase in cAMP, activation of PKA, and phosphorylation of proteins that stimulate glucose output. Studies in primary mouse hepatocytes and in mice in vivo demonstrated that biguanides disrupted the hepatic glucagon signaling cascade. In primary mouse hepatocytes, phenformin and metformin inhibited glucagon-induced accumulation of cAMP and subsequent phosphorylation of PKA cellular protein targets. Biguanides specifically inhibited endogenously synthesized cAMP and prevented PKA-dependent phosphorylation in response to glucagon, but not PKA activation and target protein phosphorylation caused by a membrane-permeable cAMP analog. Further, biguanides inhibited glucose output in hepatocytes treated with glucagon, but not in cells treated with the cAMP analog. On the basis of these observations, the authors suggest that biguanides target glucagon signaling upstream of PKA. Additional experiments showed that metformin treatment led to elevated levels of intracellular AMP, which, in turn, inhibited glucagon-stimulated adenylyl cyclase activity and lowered cAMP levels. The authors next studied the effects of biguanides in mice to determine their functional effects in vivo. In glucagon-stimulated mice, metformin halted the glucagon-stimulated increase in cAMP, PKA activation, and subsequent phosphorylation of PKA targets in the liver. These studies highlight the role of glucagon-induced adenylate cyclase activity in type 2 diabetes. The authors emphasize the importance of focusing on development of adenylate cyclase inhibitors as novel antidiabetic therapeutics. However, this newly proposed mechanism needs to be demonstrated in humans. — *Eileen M. Resnick, PhD*

■ Miller et al. Biguanides suppress hepatic glucagon signalling by decreasing production of cyclic AMP. Nature 2013;494:256–260

Excess Iron Suppresses Adiponectin and Leads to Insulin Insensitivity

Excess iron stores have been linked to increased risk of type 2 diabetes, but the mechanism underpinning this association is unknown. Although serum ferritin responds to inflammatory stress, a hallmark of diabetes, iron may also increase diabetes risk via alternate mechanisms. Excess iron is associated with impairment of pancreatic β-cell function and decreased insulin secretion and sensitivity, and it is negatively correlated with adiponectin levels. Considering that decreased levels of adiponectin, an insulin-sensitizing cytokine, are correlated with obesity, type 2 diabetes, and insulin resistance, new studies from Gabrielsen et al. sought to determine a mechanistic connection among iron excess, decreased adiponectin, and type 2 diabetes. Experiments in humans showed a negative correlation between serum ferritin and adiponectin, and this relationship was more pronounced in diabetic individuals. In these individuals, serum ferritin levels were two times higher and adiponectin levels were 24% lower than in nondiabetic individuals. Similar correlations were observed in people with the metabolic syndrome, especially those with diabetes. Companion studies in mice showed that serum adiponectin levels were 29% lower in mice fed a high-iron diet compared with those fed normal chow, whereas a restricted iron diet increased adiponectin levels by 31%. In addition, maximal glucose disposal rate was significantly decreased in mice on iron-rich diets. Adiponectin mRNA decreased by 30% in adipocytes treated with iron sulfate—a result the authors attribute to iron's ability to downregulate FOXO1 transcription factor activity. Further, studies in knockout mice analyzed the role of the iron channel protein, ferroportin, and showed that adipocyte-specific loss of ferroportin led to increased iron adipocyte levels and decreased adiponectin mRNA. The same studies showed that insulin resistance increased and glucose tolerance decreased. In humans with high-normal serum ferritin and impaired glucose tolerance, phlebotomy lowered serum ferritin, led to increased adiponectin, and improved glucose tolerance. The authors concluded that iron's effects on metabolic syndrome are via adipocyte iron stores and adiponectin, rather than systemic inflammation. Further clinical trials are required to evaluate how iron reduction may benefit individuals with diabetes and metabolic syndrome. — *Eileen M. Resnick, PhD*

■ Gabrielsen et al. Adipocyte iron regulates adiponectin and insulin sensitivity. J Clin Invest 2012;122:3529–3540

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