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Highlights From the Latest in Diabetes Research

The Relationship Between Obesity and Vitamin D Deficiency: Causation Determined?

Multiple investigations have evaluated the relationship between obesity and vitamin D deficiency, two modifiable factors that contribute to the risk of several chronic diseases. While such studies have identified a strong association between these phenotypes, it has been difficult to determine causality and the direction of the association. Through a series of sophisticated genetic analyses including bi-directional Mendelian randomization (MR), results from Vimaleswaran et al. have highlighted potentially important insights regarding the link between obesity, as assessed by BMI, and vitamin D deficiency. Using meta-analysis approaches in approximately 42,000 participants of D-CarDia, the authors observed that each unit increase in BMI was associated with a 1.15% decrease in 25-hydroxyvitamin D [25(OH)D]. In order to infer causality, their findings were extended by MR using previously established BMI-related ($n = 12$) and vitamin D–related ($n = 4$) single nucleotide polymorphisms in order to generate allele scores for the analyses. These analyses revealed that while the BMI allele score was significantly associated with reduced 25(OH)D levels (-0.06% [95% CI -0.10 to -0.02%], $P = 0.004$), neither the vitamin D synthesis or metabolism allele scores were associated with BMI (0.01 [-0.17 to 0.20], $P = 0.88$ and 0.17 [-0.02 to 0.35], $P = 0.08$, respectively). Using the instrumental variable (IV) ratio method, it was observed that each 10% increase in BMI led to a 4.2% decrease in 25(OH)D levels. In contrast, IV analyses did not provide evidence that 25(OH)D levels significantly affected BMI. Follow-up analyses using data from the Genetic Investigation of Anthropometric Traits (GIANT) consortium confirmed the lack of association between vitamin D allele scores and BMI. Together, these results suggest that an increase in obesity results in lower vitamin D status but that vitamin D concentration has little or no impact on the development of obesity. — *Joshua P. Lewis, PhD*

■ Vimaleswaran et al. Causal relationship between obesity and vitamin D status: bi-directional Mendelian randomization analysis of multiple cohorts. PLoS Med 2013;10:e1001383

Defective Insulin Signaling: A Common Feature of Diabetes and Alzheimer's Disease?

Obesity and aging are at the root of considerable public health concern in many developed countries: In many industrialized nations, there has been a marked increase in the prevalence of obesity over the last several decades, a trend that is occurring in tandem with the "graying" of many of the same populations. The prevalence of type 2 diabetes has increased in parallel with trends in obesity; a similar pattern is occurring for both mild cognitive impairment and Alzheimer's disease (AD) in relation to the growing number of older adults in many developed countries. There has been some research from Bomfin et al. suggesting a link between diabetes and decrements in cognition, including AD. Insulin resistance (IR) is a cardinal feature of type 2 diabetes, and there is evidence supporting the idea that IR is present in AD. Findings from recent studies suggesting that brain insulin signaling is defective in AD raise obvious questions regarding the possibility that insulin signaling defects may play a role in the development of both diabetes and AD. Building on the findings showing that amyloid-β peptide (Aβ) oligomers (AβOs) (synaptotoxins that collect in the AD brain) result in the loss of insulin receptors from neuronal tissues, new data suggest that AβOs also activate the Jun NH_2-terminal kinase/tumor necrosis factor-α (JNK/TNF-α) pathway and induce insulin receptor substrate (IRS)-1 phosphorylation in hippocampal neurons. Both JNK activation and IRS-1 phosphorylation are also observed in diabetes, indicating that pathologic mechanisms related to insulin signaling may be shared in the two conditions. The neuronal pathologies that were induced by AβOs in these experiments were prevented with exenatide. In Tg mice with a brain condition that models AD, exenatide blocked defective insulin signaling and improved cognition. Assuming that impaired insulin signaling is in the causal pathway for AD, exploration of the role of glucagon-like peptide 1 receptors may be ripe for future investigation. It is interesting to consider the idea that two of the most pressing chronic conditions affecting developed nations could be treated with the same therapeutic agent. Despite these intriguing results, it should be stressed that the new findings could merely reflect an association of two common diseases. — *Helaine E. Resnick, PhD, MPH*

■ Bomfin et al. An anti-diabetes agent protects the mouse brain from defective insulin signaling caused by Alzheimer's disease–associated Aβ oligomers. J Clin Invest 2012;122:1339–1353

Betatropin: A New Hormone Regulating β-Cell Replication and Mass

Although the defects underpinning type 1 and type 2 diabetes differ in fundamental ways, both conditions benefit from treatments that result in increased β-cell mass. Although there is a rapid increase in β-cell replication in the embryonic and neonatal stages of development, the rate of increase slows substantially in later life. However, the rate of β-cell replication can increase in response to certain challenges in late life, including gestation, pancreatic injury, and insulin resistance. The fact that both β-cell number and mass can increase in response to certain challenges raises the possibility to harness and direct mechanisms that favor β-cell proliferation in a manner that could have therapeutic implications. Although focusing on circulating factors is an appealing approach to this problem, targeting currently identified hormones is limited by the lack of specificity of these factors or their modest impact on β-cell proliferation. New work by Yi et al. provides intriguing data on a newly identified hormone that has potential therapeutic implications. In a series of experiments using a new mouse model in which β-cell replication can be induced, the investigators identified a gene that encodes a protein that is expressed in liver and fat. Importantly, this protein was found to be elevated in insulin resistance and to specifically induce pancreatic β-cell proliferation and increased β-cell mass. In addition to demonstrating its impact on β-cell mass, the newly published results indicate that insulin-resistant mice expressing the new protein experienced significant improvements in glucose tolerance. The investigators named this new hormone betatrophin. Although its mechanism of action remains unknown, the authors suggest that in the future, this hormone could serve as a companion to existing diabetes therapies or perhaps even replace the need for exogenous insulin. — *Helaine E. Resnick, PhD, MPH*

■ Yi et al. Betatrophin: a hormone that controls pancreatic β cell proliferation. Cell 2013;153:747–758

New Loci Associated With Birth Weight Identify Genetic Links Between Intrauterine Growth and Adult Height and Metabolism

Fetal growth and birth weight are associated with the development of adult-onset metabolic diseases. Both environmental insults (i.e., maternal nutrition, smoking, and drug use) and genetic factors have been implicated in alterations in intrauterine growth and development. A recent report by Horikoshi et al. investigates the genetic factors affecting birth weight through an expanded meta-analysis genome-wide association study (GWAS) aimed at identifying genetic loci that also correspond with adult height and metabolic traits. The expanded meta-analysis GWAS of birth weight (26,836 subjects of European descent from 18 studies) identified four new loci associated with birth weight and confirmed three previously identified loci. Single nucleotide polymorphisms in genes in two of the loci, *ADCY5* and *CDKAL1*, were previously shown to be associated with type 2 diabetes. At both loci, the alleles associated with lower birth weight were also associated with increased risk for type 2 diabetes, with evidence for impaired insulin secretion in the adult population. These results are consistent with a reduction in birth weight due to reduced insulin concentration, which manifests as type 2 diabetes in adulthood. The Gly389-encoding allele of a missense mutation in the *ADRB1* locus (Arg389Gly) was associated with lower birth weight and lower systolic blood pressure in adulthood. Finally, the birth weight–lowering alleles at two of the birth weight–associated loci, *HMGA2* and *LCORL*, were also associated with lower adult height. This study not only identifies genetic links between intrauterine growth and adult height and metabolism, it also sheds new light on the biological pathways and mechanisms influencing these traits and development of disease. Dissecting these biological pathways and the relationships between the intrauterine and adult presentation of disease will allow for early, personalized prevention and treatment. — *Coleen M. Damcott, PhD*

■ Horikoshi et al. New loci associated with birth weight identify genetic links between intrauterine growth and adult height and metabolism. Nat Genet 2013;45:76–82

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