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Highlights From the Latest in Diabetes Research

Midlife Fitness Associated With Compression of Morbidity in Late Life

It is widely accepted that exercise is beneficial to health, yet national survey data indicate that 36.2% of American adults do not engage in any leisure-time physical activity. Further, numerous cross-sectional and longitudinal studies have quantified relationships between physical activity and various outcomes including diabetes, cardiovascular disease, and mortality, with most showing an inverse association between fitness and these unfavorable outcomes. An interesting question that has not been investigated is the association between fitness level in midlife and nonfatal outcomes that occur at older ages and how this dynamic relates to the onset of morbidity in old age. New data from Willis et al. address these questions in a cohort of >18,000 men and women who were examined between 1970 and 2009 as part of the Cooper Center Longitudinal Study (CCLS). Participants in this intriguing study turned 65 between 1999 and 2009, and their Medicare claims data were merged with fitness and other clinical data that were collected during in-person CCLS examinations. The combination of CCLS and Medicare claims data allowed investigators to quantify the association between midlife fitness, measured by both metabolic equivalents (METs) and fitness quintiles, and the burden of eight nonfatal chronic conditions that are common in old age. These conditions included congestive heart failure, ischemic heart disease, stroke, diabetes, chronic obstructive pulmonary disease, chronic kidney disease, Alzheimer's disease, and colon or lung cancer. The data showed that in both men and women, higher quintile of midlife fitness was associated with markedly lower rates of chronic conditions in old age. In women, the rates of chronic conditions were 20.1, 16.6, 14.3, 12.3, and 11.4 per 100 person-years for the 1st to 5th quintile of midlife fitness, respectively. Although the overall chronic disease burden in older age was higher across the board in men, an identical pattern was observed with respect to midlife fitness levels. When fitness was examined as a continuous variable using METs, a significant inverse association between METs and chronic conditions was also observed. Finally, the investigators showed that higher levels of midlife fitness were associated with a delay in development of chronic conditions, indicating a compression of morbidity in old age. Against the backdrop of these results from Willis et al., it is not surprising that key objectives of Healthy People 2020 target improving physical activity levels in both children and adults. — *Helaine E. Resnick, PhD, MPH*

■ Willis et al. Midlife fitness and the development of chronic conditions in later life. Arch Intern Med. 27 August 2012 [Epub ahead of print]

Normal BMI: A New Risk Factor Among Patients With Newly Diagnosed Diabetes?

National data indicate that more than one-third of American adults are obese, an alarming figure that has far-reaching implications for development of weight-related chronic conditions in an aging society. Compounding the data on unfavorable trends in obesity is a plethora of evidence linking both diabetes and obesity with a host of unfavorable outcomes including mortality. However, it is interesting to note that new cases of type 2 diabetes occur along a continuum of BMI. Although most cases are identified among persons who are overweight or obese at the time of diagnosis, some are observed among patients with "normal" BMI (18.5 to <25 kg/m^2). Given the strong associations among obesity, diabetes, and mortality, a new study by Carnethon et al. sought to explore the relationship of this widely accepted BMI cut point in relation to mortality among people with newly diagnosed diabetes. In an ambitious series of secondary analyses, the investigators pooled data from five large cohort studies and identified 2,625 participants over age 40 years with incident diabetes. Of these, 12% had normal BMI at the time of diabetes diagnosis. These participants contributed more than 27,000 person-years of follow-up time during which 449 deaths occurred. Of these, 178 were attributed to cardiovascular causes. Relative to diabetic patients who were overweight or obese at the time of diagnosis, those with normal BMI had higher rates (per 10,000 person-years) of total (284.8 vs. 152.1), cardiovascular (99.8 vs. 67.8), and noncardiovascular (198.1 vs. 87.9) mortality. After adjustment for a number of potentially confounding factors, normal-weight diabetic individuals had a significantly higher risk of both total and noncardiovascular mortality relative to their overweight and obese counterparts. The authors speculate that the association between lower BMI at diabetes diagnosis and elevated mortality may be due to the presence of other underlying illnesses associated with weight loss, LADA or because leaner individuals may be screened less frequently for diabetes, leading to greater progression in illness by the time of diagnosis. Although the pooled data in this report did not permit detailed investigation of the many possible reasons for the association between normal BMI and mortality among diabetic individuals, low BMI at the time of diagnosis may be an easily measured and straightforward marker of elevated mortality risk among newly diagnosed patients. — H.E.R.

■ Carnethon et al. Association of weight status with mortality in adults with incident diabetes. JAMA 2012;308:581–590

Metformin: A New Candidate Therapy for Neural Injury and Degeneration

The aging of the population in the developed world has resulted in increases in both stroke and Alzheimer's disease—conditions that are characterized by neurodegeneration and injury. Novel strategies to promote recruitment of neural stem cells to sites of injury or degeneration would be valuable therapeutic tools to meet these growing public health concerns. New data indicate that metformin, a commonly prescribed oral therapy for type 2 diabetes, stimulates neurogenesis via the same signal transduction pathway that is activated in liver cells. Wang et al. examined the molecular mechanism driving metformin's enhancement of neurogenesis using a variety of experiments involving murine cultured cells, in vivo studies, a behavioral water maze task, and human embryonic stem cells (hESCs). First, knockdown studies using radial precursors from cultured embryonic murine cortex cells showed that signaling through the atypical protein kinase Cζ(aPKCζ) isoform, with subsequent activation of the transcriptional coactivator and histone acetyltransferase CBP, enhanced neurogenesis. Building on the knockdown studies, the authors confirmed that metformin enhanced neurogenesis via the PKC-CBP cascade in embryonic cortical precursors in vitro. Similar results were shown in forebrain precursors from hESCs, thereby providing evidence that metformin may eventually be used to activate neurogenesis in human neural precursors. The authors also studied metformin's regulation of neurogenesis in adult mice. Neurogenesis was enhanced in hippocampal slices from mice treated with metformin, and this effect was found to be CBP dependent in vivo. Compared to wild-type CBP mice, those heterozygous for CBP did not exhibit metformin-enhanced neurogenesis. Because adult neurogenesis in the hippocampus is important for spatial memory, the authors developed a behavioral water maze paradigm to assess metfomin's effects on spatial memory learning. Adult mice injected with metformin had enhanced spatial memory and long-term neurogenesis compared with controls, providing evidence for metformin's functional relevance. The authors suggest that metformin's effects on neurogenesis and hippocampus-dependent spatial memory in adult mice are especially relevant to stroke and Alzheimer's disease, in which the hippocampus plays an important role. Recruitment of adult neural stem cells to areas of injury or degeneration may represent an attempt at neural repair. The authors reason that metformin could be used to enhance the neurogenic activity of endogenous adult stem cells in patients with Alzheimer's disease because many of these patients also suffer from diabetes, a possible promoter of neurodegeneration. — *Eileen M. Resnick, PhD*

■ Wang et al. Metformin activates an atypical PKC-CBP pathway to promote neurogenesis and enhance spatial memory formation. Cell Stem Cell 2012;11:23–35

Neutrophil Elastase Is a Key Player in Inflammation, Obesity, and Insulin Resistance

Immune cells such as macrophages, T cells, B cells, mast cells, and eosinophils are present in adipose tissue (AT) from mice with diet-induced obesity (DIO) and have been implicated in the development of obesity and insulin resistance. Neutrophils produce chemokines and cytokines, and they also secrete neutrophil elastase, a protease involved in sterile inflammation. As a result, neutrophils are another immune cell type that may play a role in the development of inflammation-induced insulin resistance. To assess the potential role of neutrophil elastase in insulin resistance, Talukdar et al. compared mice on a high-fat diet (HFD) that develop DIO with those that were fed chow. AT from HFD-fed mice expressed more neutrophils and neutrophil elastase and also had higher neutrophil elastase activity compared with chow-fed mice. Additional studies used mice lacking the gene for neutrophil elastase (NEKO mice) and showed that NEKO mice on the HFD regimen were protected from its inflammatory effects. In fact, NEKO mice had higher glucose tolerance, lower fasting insulin concentrations, and 90% lower neutrophil content in AT compared with wild-type (WT) HFD mice. Next, the authors explored the effect of neutrophil elastase on insulin signaling. Compared with WT mice, NEKO mice exhibited higher levels of insulin-stimulated phosphorylation of the insulin signaling biomarker Akt in both AT and liver. Another key insulin signaling protein, insulin receptor substrate 1 (Irs1), is degraded by neutrophil elastase. Levels of Irs1 in the liver and AT were higher in NEKO compared with WT mice. Administration of neutrophil elastase to primary mouse and human hepatocytes led to decreased levels of Irs1 and insulin-stimulated Akt phosphorylation. To determine whether the observed changes in insulin signaling resulted in functional outcomes, the authors measured glucose output in primary mouse hepatocytes +/- neutrophil elastase treatment. Neutrophil elastase prevented insulin from inhibiting glucagon-stimulated hepatocyte glucose output. Data in this report also demonstrated decreases in expression of lipogenic genes, liver lipids, and proinflammatory factor mRNAs and an increase in anti-inflammatory factors in liver and AT of NEKO mice compared with WT. The proinflammatory effects of neutrophil elastase were dependent on the Toll-like receptor 4 (Tlr4). The authors suggest that neutrophils, and specifically neutrophil elastase, play a prominent mechanistic role in obesity-induced inflammation by causing insulin insensitivity at the cellular level. — *E.M.R.*

■ Talukdar et al. Neutrophils mediate insulin resistance in mice fed a high-fat diet through secreted elastase. Nat Med. 5 August 2012 [Epub ahead of print]

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