Editorial

The Metabolic Syndrome and Aging

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In 1966, Camus first described the concept of the metabolic syndrome (1). From 1988 onwards, the importance of the metabolic syndrome was popularized by Reaven (2). The metabolic syndrome consists of a deadly quintet of factors, namely diabetes, hypertension, hyperuricemia, lipid abnormalities, and alterations in thrombosis potential, that are associated with hyperinsulinemia and insulin resistance. The metabolic syndrome is directly related to increased atherogenesis and death from myocardial infarction. The metabolic syndrome is directly related to the accumulation of visceral adiposity in middle age associated with overeating and a decline in exercise. In addition, there appears to be a genetic predisposition to developing the metabolic syndrome. The metabolic syndrome could be conceived as the “couch potato” syndrome (Figure 1). It has been estimated that 15% to 20% of persons aged over 70 years have the metabolic syndrome.

Banks and colleagues (3) studied a subset of wild baboons (Papio cynocephalus) that foraged from a trash heap in the Kenyan savannah. Some of this tribe of baboons developed hyperleptinemia, hyperinsulinemia, hyperglycemia, elevated insulin/glucose ratios, and increased cholesterol. Others in the same tribe developed hypercholesterolemia but none of the signs of insulin resistance. This demonstrated the importance of the interaction of genetic predisposition with the environment in the pathogenesis of the metabolic syndrome.

Besides insulin, two other hormones have been associated with the development of the metabolic syndrome. These are leptin and adiponectin. Both are peptide hormones produced from adipose tissue. Leptin levels closely follow the amount of total adiposity (4,5). Leptin produces anorexia and increased metabolism, thus attempting to decrease the increased adiposity (6). Testosterone decreases leptin levels in males and leads to a decline in body fat (7,8). Thus, the age-related decline in testosterone in males may play a role in the pathogenesis of the metabolic syndrome (9). With increasing obesity, resistance to the effects of leptin occurs. This resistance appears to be due to hypertriglyceridemia.

Adiponectin has been shown to enhance insulin sensitivity and decrease triglycerides (10). Low levels of adiponectin are closely associated with the development of insulin resistance. Trunkal fat is associated with increased cytokines such as interleukin-6 and tumor-necrosis factor α (11). These two cytokines play a role in the development of insulin resistance. Testosterone inhibits the production of interleukin-6, again supporting a minor role for the andropause in the development of the metabolic syndrome (12).

Numerous recent studies have shown that hypertension is especially lethal in diabetics. Both the SHEP (Systolic Hypertension in Elderly Persons) and the Syst-Eur Trial found an almost doubling of mortality risks in older diabetics with systolic hypertension (13,14). The UKPDS (United Kingdom Prospective Diabetes Study) found that treating blood pressure produced better risk reduction than did treating diabetes (15). In the HOPE (Heart Outcomes and Prevention Evaluation) and CAPP (Captopril Prevention Project) trials, angiotensin-converting enzyme inhibitors had a better effect on lowering cardiovascular events in diabetics compared with nondiabetics (16,17). In addition, in the SCOPE (Study on Cognition and Prognosis in the Elderly) trial angiotensin receptor blockers decreased new onset diabetes by 20% (18). Coronary artery disease can be characterized as the diabetic’s sword of Damocles. It is clear that diabetics require aggressive treatment to prevent atherosclerosis.

The DIGAMI (diabetes mellitus, insulin glucose infusion in acute myocardial infarction) studies examined 620 persons with diabetes who developed a myocardial infarction (19). The mean age was 68 years. They provided intensive glucose-lowering therapy in all participants with a glucose equal or greater than 11 mmol/L. In a 3.4 year follow-up, they found a reduction in mortality, with only 9 persons being the number needed to treat to prevent 1 additional death.

In this issue of the Journals, Rasgon and Jarvik (20) suggest that dementia and depression should be considered, in some cases, to be due to the metabolic syndrome. A number of commentators have taken issue with some of their hypothesis while agreeing with other components (21–24). Recently, in-depth reviews of the pathogenesis of dementia and its associated behaviors (25–27), as well as of depression (28), have appeared in the Journals.

The causes of cognitive decline in diabetes are complex and multifactorial. It is clear that diabetics in older persons is associated with a worse cognitive function compared with those who have normal cognition (29,30). Gregg and colleagues (31) followed 682 women aged 72 years with diabetes and found a two-fold increase in cognitive impairment over this period. Numerous studies have shown that not only do older diabetics have cognitive impairment, but that they also have excess functional decline (32–38).
A number of studies have shown that hyperglycemia per se produces cognitive dysfunction and that cognition is improved when glucose is lowered (39–41). Also, persons with the metabolic syndrome are more likely to have small infarcts and develop vascular dementia, (42–44) as are persons with hypertension (45–48). Glucoregulatory hormones such as amylin (49) and glucagon-like peptide I (50) are modulators of memory.

As shown in a forthcoming article by Zamboni and colleagues leptin levels are closely related to the metabolic syndrome in older women (51). Leptin receptor-deficient animals have impaired spatial memory and long-term potentiation in CA1 of the hippocampus, suggesting that leptin is a powerful memory enhancer (52).

In Type II diabetes, elevated triglycerides are associated with poor performance on the digit symbol substitution test, digit span backward test, and reaction time (53). In another study, elevated triglycerides were associated with poor semantic memory (54). Reducing hypertriglyceridemia with gerrifibrozal improved both cerebral blood flow and function on the cognitive capacity screening examination (55). Plasma high-density lipoprotein levels are correlated with cognition in persons with exceptional longevity (56). Elias and colleagues (57) found that obesity and hypertension are independently related to impaired cognition on a battery of cognitive tests. These studies support the hypothesis that cognitive dysfunction should be considered a part of or a consequence of the metabolic syndrome.

The concept that the metabolic syndrome directly leads to Alzheimer’s disease is intriguing. Clearly, small vascular infarcts can lead to cytokine production, which may stimulate beta-amyloid production (58), and low testosterone levels that occur in diabetes may be associated with overproduction of beta-amyloid (59,60). Beta-amyloid overproduction appears central to the pathogenesis of Alzheimer’s disease, not only by directly decreasing memory (61–63) but also by leading to the overproduction of free radicals (64). Hyperglycemia and hypertriglyceridemia can interact with the amnestic effects of beta-amyloid to cause a more rapid decline in cognition, and diabetes accelerates free radical production.

Depression has been shown to lead to poor outcomes in older diabetics (65). This is predominantly due to the poor compliance associated with depression. Persons with depression often have elevated cortisol levels, which can lead to hyperglycemia and hypertension (66). Persons who have cerebral vascular accidents are more likely to suffer major depression (28). Persons with depression have poorer outcomes when they have a myocardial infarction and are more likely to have a subsequent myocardial infarction (28). Depression is obviously closely related to the metabolic syndrome, but which is the chicken and which is the egg remains uncertain.
While some of the “merchants of immortality” continue to search for the Holy Grail of longevity (67–69), it is clear that the physician who practices evidence-based medicine and avoids errors already has many of these tools in his or her grasp (70–72). Diabetes accelerates damage to the DNA (73). It is now becoming clear that rigorous treatment of the metabolic syndrome when it first emerges in middle age represents not only a key to life prolongation, but also to extended number of quality-adjusted life years that a person will experience. As has so often been pointed out in the Journals, exercise, particularly resistance exercise, represents an important component of the treatment to slow aging by reducing the prevalence of the metabolic syndrome and decreasing cognitive and depressive syndromes (74–77). As always, the appropriate care of older persons requires an interaction of “high touch” and “high tech.”

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