See accompanying article by Scholze et al., p. 1617

So, Is Leptin Good or Bad in Chronic Kidney Disease?

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In the general population, leptin inhibits appetite and increases energy expenditure. Many obese individuals, however, may have inappropriately high levels of circulating leptin. This is generally attributed to hyporesponsiveness to leptin in obesity (1). Leptin is a member of the interleukin-6 family of proinflammatory cytokines. It is cleared from the circulation by the kidney through both glomerular filtration and metabolic degradation in the renal tubules (2). Leptin gene expression in adipose tissue of individuals with chronic kidney disease (CKD)[1] is decreased, which may be a compensatory mechanism vis-à-vis decreased clearance. Positive correlations between leptin and C-reactive protein concentrations in CKD suggest the role of inflammation as a contributor to hyperleptinemia (3), especially because inflammatory cytokines are associated with anorexia in dialysis patients (4). In subtotally nephrectomized *db/db* mice, a model of leptin receptor deficiency in CKD, leptin has been shown to contribute to uremic cachexia through signaling through its receptor (5). In some observational studies, increased serum leptin concentrations were observed in dialysis patients who lost lean body mass (6–8) or had hypoalbuminemia with low protein intake (9). In patients with CKD, correction of metabolic acidemia, a possible activator of ubiquitin-proteasome induced cachexia (10), is associated with an increase in serum leptin levels (11,12).

There are, however, an increasing number of contradictory studies that suggest a paradoxically inverse association between higher serum leptin and improved markers of nutritional status and outcome in CKD (13,14). Indeed, leptin, similar to serum albumin, has been reported to be a negative acute phase reactant in patients with CKD (13). Administration of growth hormone (15,16) and appetite stimulators such as megestrol acetate (17) to dialysis patients increase plasma leptin levels. Iglesias et al. (15) and Aguilera et al. (18) found a strong direct correlation between serum leptin and both BMI ($r = 0.70$) and triceps skinfold thickness ($r = 0.77$) in dialysis patients. Higher leptin levels were also associated with higher serum lipid, healthier clinical characteristics, a lower clinical atherosclerosis score, and better appetite (15,18). In non-obese dialysis patients (BMI < 25 kg/m^2), there were direct correlations between serum leptin and markers of nutritional status, including serum albumin ($r = 0.63$), transferrin ($r = 0.40$), and cholesterol ($r = 0.65$) (15,18). Nasri et al. (19) reported a significant positive correlation between better left ventricular function (ejection fraction) and logarithm of serum leptin ($r = 0.32$). Hence, it was expected, but not yet shown, that a high serum leptin may be associated with better survival in dialysis patients (20).

In this issue of *Obesity*, Scholze et al. (21) studied 71 hemodialysis patients for almost 7 years and showed that baseline serum leptin levels were lower in deceased patients compared with the survivors. The 3.8 times higher risk of death among patients with a serum leptin concentration below the median indicates that serum leptin can be yet another so-called "counterintuitive" predictor of mortality in CKD. Similar patterns that have been observed in both dialysis and chronic heart failure populations include the "obesity paradox" (22,23), the "hypercholesterolemia paradox" (24), and the "homocysteine paradox" (25). These counterintuitive constellations, together also known as "reverse epidemiology" (26), can be a result of survival selection—because many patients with CKD die before reaching end-stage (dialysis-dependent) status, or they may be related to the time discrepancy between the two sets of risk factors, i.e., overnutrition (long-term killer) vs. undernutrition (short-term killer) (20). Apart from their etiology, the said survival paradoxes may exist in more than 20 million Americans with chronic disease states or with advanced age (27). Hence, a provocative and seemingly time-inappropriate question would be whether obesity, hypercholesterolemia, or hyperleptinemia should be allowed or even encouraged in individuals with chronic disease states who are

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[1] Nonstandard abbreviation: CKD, chronic kidney disease.

prone to imminent cachexia and poor survival. Even though leptin administration seems promising in patients with lipodystrophy (28), at this point in time, it is too early to postulate that the administration of leptin would improve longevity in individuals with chronic disease states including advanced CKD. Nevertheless, studying obesity, hyperlipidemia, and hyperleptinemia in dialysis patients as the archetypical population with such reverse epidemiology may lead to the development of population-specific guidelines and treatment strategies beyond the current Framingham cardiovascular risk factor paradigm. These hypotheses and efforts, however, should never distract us from our ongoing campaign against obesity and its untoward metabolic and cardiovascular consequences in the relatively healthy general population.

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