Higher Plasma Levels of Adiponectin in Hemodialysis Patients: Good or Bad?

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Adiponectin is a secretory and collagen-like plasma protein of adipose tissue (1) that is known to play an important role in the development of metabolic syndrome. Plasma levels of adiponectin are significantly decreased in obesity, type 2 diabetes mellitus, coronary artery disease (CAD) and chronic kidney disease (CKD). Adiponectin has anti-inflammatory effects through nuclear factor- κ B. It also downregulates adhesion molecule expression on endothelial cells and enhances lipid clearance. These rescue mechanisms protect against the progression of CAD and CKD. Although a lower level of adiponectin may be considered to be an independent risk factor for CAD and CKD, the association between adiponectin levels and mortality remains controversial.

Cardio-renal Syndrome

Heart failure (HF) and renal dysfunction frequently coexist. This is referred to as the cardio-renal syndrome. This syndrome represents the sum total of an adversarial relation and is clinically manifest as worsening renal function. Despite the growing recognition of the frequent presentation of this syndrome, its underlying pathophysiology is not well understood. Adiponectin may also be associated with cardio-renal syndrome. In fact, a lower level of adiponectin is considered to be an independent risk factor for CAD, and is associated with patients with acute coronary syndrome (2) and coronary complex lesion in stable CAD (3). Furthermore, in patients with CKD, hypoadiponectinemia is a novel putative cardiovascular risk factor in patients with mild and moderate renal failure (4). Thus, lower plasma levels of adiponectin might play an important role in the pathogenesis of cardio-renal syndrome. On the other hand, the adiponectin concentration is increased when renal function declines. Guebre-Egziabher et al indicated that the increase in adiponectin may be explained by the patients' body composition and the altered metabolic profile (e.g. serum leptin) that occurs with the impairment of renal function (5). Actually, this situation

is more complicated. It is not known whether this increase in adiponectin reflects impaired adiponectin clearance by the kidney or whether it is a compensatory mechanism aimed at counteracting increased CAD risk factors.

Adiponectin Levels in Hemodialysis (HD) or HF Patients

Adiponectin has both anti-atherogenic and anti-inflammatory properties. Adiponectin protects against the development of systolic dysfunction after myocardial infarction in adiponectin-deficient mice (6). Adiponectin is also a key regulator of albuminuria, likely through the AMP-activated protein kinase pathway to modulate oxidant stress in podocytes in adiponectin-deficient mice (7). These reports have provided data to support the notion that adiponectin is essentially cardio- and renal-protective. Therefore, higher plasma adiponectin levels should be associated with a decreased risk of mortality in HD patients.

Circulating adiponectin concentrations may be associated with the occurrence of coronary in-stent restenosis in end-stage renal disease (ESRD) patients undergoing maintenance HD (8). The consumption of circulating adiponectin may be needed to prevent coronary restenosis after stent implantation to induce a reduction in adhesion molecule expression. Until recently, it has been unclear whether adiponectin is associated with HD. Ohashi et al reported in *Internal Medicine* (9) that higher, rather than lower, plasma adiponectin levels independently predicted total mortality in HD patients. A Cox-hazards multivariate regression analysis adjusted for conventional case-mix features (age, sex, and underlying CKD) indicated that the serum level of adiponectin was a significant determinant of all-cause mortality. There was a 10.3% risk increment for each 1 μ g/mL increase in adiponectin during the 3-year follow-up.

With regard to HF, although higher plasma adiponectin levels should be associated with a decreased risk of mortality in patients with chronic HF (CHF), plasma adiponectin

levels are associated with an increased risk of mortality in patients with CHF (10) and an increase according to the severity of CHF (11). Thus, higher adiponectin may be a critical risk factor for mortality and the severity of CHF. Higher plasma adiponectin levels predict mortality in patients with CHF or HD, while hypo adiponectinemia might be a risk factor for the onset or progression of cardio-renal diseases.

Cardiovascular Mortality in CKD Patients

The report of Ohashi et al report also indicated that 15 patients had died by the end of the follow-up period (9). The cause of death included CAD in only 3 (20%). In the remaining cases, the cause of death was infection (n=5, 33%), malignancy (n=2, 13%), cerebrovascular disease (n=1, 7%) and other (n=4, 27%). Although adiponectin levels were an independent predictor of total mortality, the percentage of deaths caused by CAD was relatively low in this study. This may be due to the fact that only a few patients died (n=15). In this regard, it is not clear whether a higher level of adiponectin is a risk factor for mortality by CAD in CKD. A recent cohort study showed that a 1 µg/mL increase in adiponectin was associated with a 3% increased risk for all-cause mortality and a 6% increased risk for cardiovascu-

lar mortality in moderate CKD patients (12). On the other hand, plasma adiponectin levels were significantly lower among patients who experienced new cardiovascular events than among event-free patients in patients with ESRD (13). In addition, there was a 3% reduction in risk for each 1 µ/mL increase in plasma adiponectin levels, and the relative risk of adverse cardiovascular events was 1.56 times higher among patients in the first adiponectin tertile (adiponectin ≥ 16.4 µg/mL), compared to those in the third tertile (adiponectin < 16.4 µg/mL) in patients with ESRD (11). Although the association between adiponectin levels and mortality remains unclear, adiponectin may be upregulated if it has cardio- and renal- protective roles.

Conclusions

Although CAD is the primary cause of death in patients with ESRD, the association between adiponectin levels and mortality remains controversial. The role of adiponectin under a chronic wasting state, such as in ESRD or HD patients, may be different from that in patients with mild to moderate CKD. We must reconsider the role of plasma adiponectin in each stage of renal disease.

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