Adiponectin and Leptin in Kidney Disease Patients

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Introduction

Adiponectin is a type of adipokine, namely, a hormonally active molecule secreted by adipose tissue with pervasive effects on multiple organ systems. In the general population, adiponectin has demonstrated anti-inflammatory and cardioprotective properties, and a number of studies have shown that higher levels are associated with favorable cardiovascular outcomes and survival (Table 20.1). However, in patients with non-dialysis-dependent (NDD) and dialysis-dependent chronic kidney disease (CKD), higher adiponectin levels have been paradoxically associated with adverse cardiovascular outcomes and higher mortality risk (Table 20.2). Similarly, leptin is an adipokine which has been identified as having an important role in the regulation of inflammation and energy metabolism. In the general population, high serum leptin has been associated with adverse cardiovascular outcomes, but these observations are in contradistinction to findings observed in patients with end-stage renal disease (ESRD). The objective of this chapter is to review and discuss the existing body of evidence examining the interrelationships of adiponectin and leptin and outcomes in the general population as well as in those with varying degrees of impaired kidney function.

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Adiponectin

Background Physiology

Adiponectin is a 240-amino acid hormone produced exclusively by adipose tissue, and it is encoded by the APM1 gene located on chromosome 3q27 as the most abundantly transcribed gene in adipocytes [17]. Adiponectin circulates in high concentrations ranging from 5 to 30 μg/mL, and it accounts for 0.01% of total serum proteins [18]. Adiponectin is synthesized as a monomer of 28–30 kDa, and it is assembled into trimer, hexamer (low molecular weight [LMW]), and high molecular weight (HMW) forms, with LMW adiponectin as the predominant isoform in circulation. HMW adiponectin levels as well as the ratio of HMW adiponectin to total adiponectin have been found to be strong predictors of insulin sensitivity in comparison with adiponectin monomers alone [19, 20].

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Table 20.1 Studies of adiponectin and cardiovascular disease in the general population

Study	Study population	Adiponectin	*N*	Age (years)	Study type	Follow-up	Primary outcome	Results	Conclusion
Matsuda et al. [1]	CAD risk factors undergoing CT coronary	Serum adiponectin	298	67 ± 10.3	Cross-sectional	–	Multivessel coronary disease by CT coronary	ADPN in addition to risk factors predictive of CAD (AUC 0.72; 95%CI 0.66–0.77)	APDN is risk factor for multivessel CAD
Kawagoe et al. [2]	Known CAD undergoing PCI for LAD lesion	Intracoronary adiponectin	48	65 ± 11, 69 ± 11	Prospective	66 mos	Cardiovascular event occurrence	OR 5.25 for CV event in ADPN negative group	ADPN protective against CV events
Yoon et al. [3]	CAD risk factors	Serum adiponectin	1033	57.17 ± 7.16 55.40 ± 7.29	Cross-sectional	–	Carotid intima-media thickness	OR for CIMT thickening 0.42 in men; 0.47 in women	ADPN protective against atherosclerosis
Yamashita et al. [4]	Non-DM undergoing cardiac catheterization	Serum adiponectin	97	66.2 ± 8.4	Cross-sectional	–	CAD	Low ADPN HR 3.47 (1.27–9.89) for CAD	Low ADPN increases risk for CAD severity
Komura et al. [5]	Known CAD ± DM	Total ADPN, HMW ADPN	186	64.2 ± 0.9 non-DM; 63.2 ± 1.1 DM	Cross-sectional	–	Risk factors for CAD	HMW ADPN correlates to HDL	ADPN correlates to CAD risk factors
Pischon et al. [6]	Health Professionals Follow-up study with MI during follow-up	Serum adiponectin	266	65.2	Nested case control	6 yrs	Fatal and nonfatal MI and coronary heart disease	Highest quintile ADPN lowest risk for MI (RR 0.56; 95% CI 0.32–0.99)	ADPN protective against CVD

Abbreviations: *CAD* coronary artery disease, *CT* computed tomography, *ADPN* adiponectin, *PCI* percutaneous coronary intervention, *LAD* left anterior descending, *mos* months, *CV* cardiovascular, *CIMT* carotid intima-media thickness, *DM* diabetes, *HMW* high molecular weight, *MI* myocardial infarction, *yrs* years

Table 20.2 Studies of adiponectin, cardiovascular disease, and survival in non-dialysis-dependent chronic kidney disease, dialysis, and kidney transplant recipient populations

Study	Study population	*N*	Age (years)	ADPN measurements	Follow-up	Primary outcome	All-cause mortality HR (95% CI)	Total CVD HR (95% CI)	Conclusion
Imawashi et al. [7]	NDD-CKD	150	67.7 ± 0.8	Baseline	31.9 ± 1.5 mos	CVD	–	0.86 (0.75–0.96)	Low adiponectin predictor of CVD
Menon et al. [8]	NDD-CKD	585	52 ± 12	Baseline	10 yrs	All-cause mortality, CVD	1.03 (1.01–1.05)	1.06 (1.03–1.09)	High adiponectin associated with increased mortality
Jorsal et al. [9]	NDD-CKD	438	42.3 ± 10.4	Baseline	8.1 yrs	All-cause mortality, CVD	1.75 (1.47–2.10)	1.50 (1.26–1.78)	High adiponectin associated with increased all-cause and CV mortality
Zoccali et al. [10]	HD	227	59.9 ± 15.0	Baseline	31 ± 13 mos	All-cause mortality, CVD	–	0.97 (0.93–0.99)	High adiponectin associated with decreased CV events
Diez et al. [11]	HD + PD	184	67.8 ± 11.7 52.1 ± 16.9	Baseline +12 months	33.9 ± 15.7 mos	All-cause mortality, CVD	0.68 (0.49–0.95)	0.43 (0.21–0.86)	High adiponectin associated with decreased all-cause and CV mortality
Takemoto et al. [12]	HD	68	58.8 ± 13.6, 61.0 ± 8.2	Baseline	8 yrs	All-cause mortality, CVD	–	Men: 0.74 (0.57–0.97) women: 0.79 (0.67–0.94)	High adiponectin associated with decreased CV events but not overall mortality
Abdallah et al. [13]	HD	133	54.6 ± 17.3	Baseline	24 ± 9 mos	All-cause mortality, CVD	1.17 (1.08–1.28)	1.23 (1.11–1.32)	Low adiponectin associated with increased CV events
Drechsler et al. [14]	HD	1255	65.7 ± 8.3	Baseline +182 day follow- up	3.96 yrs	All-cause mortality, CVD	1.09 (1.06–1.57)	1.33 (1.05–1.69)	Rising adiponectin associated with increased risk for mortality, CVA, MI
Rao et al. [15]	HD	176	62.2 ± 12.3	Baseline + yearly	3.96 yrs	All-cause mortality, CVD	1.08 (1.00–1.17) for baseline; 1.04 (1.01–1.07) for time dependent	–	Lower baseline adiponectin associated with prevalent CV disease. Non-linear association of adiponectin with mortality and CV outcomes.
Alam et al. [16]	Posttransplant	987	51 ± 12.8	Baseline	51 mos	All-cause mortality, graft failure	1.44 (1.13–1.85)	–	High adiponectin associated with increased all-cause mortality and graft failure

Abbreviations: *ADPN* adiponectin, *CVD* cardiovascular disease, *NDD-CKD* non-dialysis-dependent chronic kidney disease, *HD* hemodialysis, *CV* cardiovascular, *PD* peritoneal dialysis, *CVA* stroke, *MI* myocardial infarction

Adiponectin mediates its intracellular effects through the adenosine monophosphate-activated protein kinase (AMPK) pathway. Adiponectin exhibits its intracellular effects via two receptors, namely, ADIPOR1 and ADIPOR2, each of which contain seven transmembrane domains and are transmembrane G-protein receptors. ADIPOR1 has a high affinity for HMW adiponectin, while AdipoR2 has intermediate affinity for all adiponectin isoforms. ADIPOR1 is expressed primarily in the skeletal muscle, while ADIPOR2 is expressed in the liver [21]. ADIPOR1 induces extracellular calcium influx that allows for the activation of calmodulin-dependent protein kinase kinase (CaMKK) and AMPK which are further involved in the control of energy metabolism. AdipoR2 activates and increases expression of peroxisome proliferator-activated receptor α (PPAR-α) ligands and increases energy consumption [21]. Single nucleotide polymorphisms have been identified in the promoter region of both ADIPOR1 and ADIPOR2 adiponectin receptors, and homozygous individuals have been observed to have overall greater abdominal obesity versus non-homozygous individuals.

Interaction Between Adiponectin and the Kidney

ADIPOR1 and AMPK are expressed in the kidney, and adiponectin is renally excreted in healthy individuals [21]. Animal data suggest that adiponectin may have an anti-inflammatory and reno-protective role. In vitro studies using animal models showed that ADIPOR1 is expressed in glomerular endothelial cells, podocytes, mesangial cells, and Bowman's capsule epithelial cells within the glomerulus which are exposed to urinary adiponectin. Exposure of these cells to HMW adiponectin resulted in increased phosphorylation of AMPK confirming the functionality of ADIPOR1 within the glomerulus [22]. Studies of adiponectin gene knockout mice show that adiponectin accumulates in renal tissue in the setting of kidney damage. Absence of adiponectin is associated with impaired kidney function, fibrosis, albuminuria, and inflammatory response, which may be ameliorated with adiponectin repletion [23].

In human studies, cross-sectional data in type 2 diabetic patients show that urinary adiponectin concentrations are positively correlated with microalbuminuria and higher mean brachial-ankle pulse velocity, suggesting that urine adiponectin may be associated with microvascular and macrovascular disease [24]. Longitudinal studies in type 1 diabetic patients have shown that urinary adiponectin is positively correlated with albuminuria, blood pressure, and glycated hemoglobin (HbA1c) and negatively correlated with kidney function. Moreover, changes in urinary adiponectin exceeded increases in serum adiponectin suggesting a role in renal injury independent of increased glomerular filtration [25]. However, in a study of patients with CKD due to type 2 diabetes, increasing urinary HMW adiponectin levels were associated with impaired kidney function but were not associated with albuminuria [26].

Adiponectin and Cardiovascular Risk Factors

Adiponectin and Obesity

A study of Pima Indians has shown that plasma adiponectin concentrations are in fact lower in obesity [27] and are negatively correlated with body mass index (BMI), body fat percentage, waist-to-thigh ratio, fasting plasma insulin levels, and 2-hour plasma glucose concentrations [28]. Obese patients with type 2 diabetes have been shown to have decreased APM1 gene expression and mRNA transcription in adipose tissue compared to nonobese patients [29]. In contrast, weight loss leads to elevation of plasma adiponectin levels in both diabetic and nondiabetic patients [10–12, 30].

Adiponectin and Type 2 Diabetes Mellitus

Numerous studies have established an association between higher adiponectin levels and enhanced insulin sensitivity. For example, in animal studies, adiponectin has been shown to reverse insulin resistance in lipoatrophic mice, presumed to be due to the reduction of triglyceride content in muscle and liver and subsequent increase in molecules that augment fatty acid uti-

lization in muscle [31]. A systematic review and meta-analysis of 13 prospective studies have also examined the relationship between adiponectin and the risk of developing type 2 diabetes. In analyses that accounted for obesity, every 1-μg/mL increment in the log of adiponectin levels was associated with a 28% lower risk of developing type 2 diabetes (adjusted relative risk [aRR] 0.72 [95% CI] 0.67–0.78; $p < 0.001$), supporting the hypothesis that adiponectin increases insulin sensitivity in humans as well [32].

Adiponectin and Type 1 Diabetes Mellitus

A number of studies have observed that type 1 diabetic patients have higher adiponectin concentrations. In a substudy of the Coronary Artery Calcification in Type 1 Diabetes (CACTI) prospective cohort, 86 type 1 diabetic patients underwent hyperinsulinemic-euglycemic clamp testing in order to investigate the role of adiponectin in insulin sensitization. Results showed that type 1 diabetic patients had higher mean total adiponectin levels (12.3 ± 5.8 vs. 9.6 ± 5.5 μl/ml, respectively; p=0.03) and higher mean HMW adiponectin levels than their nondiabetic controls (6.5 ± 4.6 vs. 4.4 ± 3.5 μl/ml, respectively; p= 0.02) and that for any given level of adiponectin, type 1 diabetic patients had decreased insulin sensitivity compared to their nondiabetic controls as manifested by a lower glucose infusion rate [33].

Observational studies suggest that higher adiponectin levels in type 1 diabetic patients are associated with higher risk of microvascular complications including retinopathy [34] and progression of diabetic nephropathy [35]. It is unclear if these complications are directly related to adiponectin or are a marker of greater insulin resistance. Nevertheless, these observations challenge the cardioprotective role of adiponectin in patients with type 1 diabetes mellitus.

Adiponectin and Cardiovascular Disease

A number of studies have sought to examine the relationship between adiponectin and cardiovascular disease (Table 20.1). Existing data strongly suggest that adiponectin has anti-atherogenic and anti-inflammatory roles. In cellular and vascular injury, serum adiponectin levels are elevated and directly linked to vascular intima specific collagen [36]. Human studies have shown that diabetic patients with underlying coronary disease have lower adiponectin levels compared to the general population and diabetics without coronary disease [30]. Adiponectin also increases COX-2 in endothelial cells [37]. In addition, adiponectin levels were observed to inhibit expression of cell adhesion molecules suggesting a role in downregulation of inflammatory response [38]. In vitro studies suggest that adiponectin has a central role in vasodilation via its effect on nitric oxide (NO). Adiponectin has enzymatic regulation of endothelial nitric oxide synthase (eNOS) via a host of different mechanisms including increasing mRNA stability, increasing Ser1179 phosphorylation, and associating with scaffolding proteins [39].

In response to in vitro studies that suggest that adiponectin serves a cardioprotective function, population-based studies have examined adiponectin's impact on the development of coronary vascular disease. For example, in a cross-sectional study of 298 patients, Matsuda et al. looked at multivessel coronary disease on CT coronary angiography (CTCA) in relationship to adiponectin levels [1]. In this study, low adiponectin, along with four other traditional risk factors for coronary artery disease including age, sex, high triglyceride levels, and diabetes mellitus, were noted to have predictive values for multivessel disease found on CTCA (ROC analysis, AUC 0.72; 95% CI, 0.67–0.78). In addition, low adiponectin was noted to be associated with multivessel disease independent of the other risk factors. However, when low HDL and abdominal obesity were accounted for, the AUC decreased and was deemed to not be predictive for coronary artery disease in this study. However, further cross-sectional studies suggest that HMW adiponectin directly correlates to serum HDL levels [5].

In another study, Yoon et al. attempted to correlate adiponectin to carotid intima-media thickness as a surrogate for atherosclerosis [3]. This cross-sectional study of 1033 Korean participants showed that at the highest quartile of adiponectin

(defined as >9.90 mg/L in men and > 13.4 mg/L in women), adiponectin was associated with reduced subclinical atherosclerosis (OR 0.42 [95% CI] 0.25–0.77 and 0.47 [95% CI] 0.29–0.75, respectively). In addition, when adiponectin was added to the risk prediction model, AUC of the ROC analysis was observed to increase by 0.025 and 0.022 in men and women, respectively, demonstrating its predictive value for carotid intima-media thickness.

Kawagoe et al., based on an earlier study suggesting that local intracoronary adiponectin influences coronary perfusion, examined intracoronary adiponectin's impact as a predictor of adverse coronary events including unstable angina, heart failure, and myocardial infarction [2]. In this study, 48 patients with left anterior descending artery stenosis requiring percutaneous coronary intervention were divided into high vs. low adiponectin groups (greater or less than 0 μg/mL at the left coronary artery, respectively). Coronary adiponectin was calculated as the plasma adiponectin level at the great cardiac vein minus the level at the orifice of the left coronary artery. Retrospective examination of patient records over a period of 66 months demonstrated a higher incidence of adverse coronary events in the low adiponectin group as compared with the high adiponectin group (7 events among 11 patients vs. 9 events among 37 patients, respectively; $p = 0.02$).

Coronary artery disease as measured directly by coronary artery angiogram in relationship to baseline adiponectin levels and metabolic syndrome was the subject of a cross-sectional study by Yamashita et al. [4]. In this analysis, 97 patients without diabetes mellitus undergoing elective coronary angiography participated in this study. In multivariate analyses, low adiponectin levels (defined as <4.5 μg/mL) were found to be a predictor of multivessel disease (OR 3.47 [95% CI] 1.27–9.89). Combination of low adiponectin with additional components of metabolic syndrome was not associated with increased incidence of multivessel coronary artery disease, but the combination of adiponectin levels >4.5 μg/mL and <3 components of metabolic syndrome were associated with decreased prevalence of multivessel coronary artery disease (OR 0.23 [95% CI] 0.09–0.56).

To further quantify the role of adiponectin in diabetes mellitus, Wu et al. conducted the first systematic review and meta-analysis of five prospective studies and one nested case-control study that examined the relationship between serum adiponectin levels and cardiovascular disease in patients with type 1 and 2 diabetes mellitus [40]. Data in type 1 diabetics showed that adiponectin was inversely related to risk of coronary heart disease, whereas studies in type 2 diabetic patients showed mixed associations between serum adiponectin concentrations and type 2 diabetes.

Adiponectin and Mortality Risk

General Population

Pischon et al. conducted a nested case-control study among 18,225 male participants from the Health Professionals Follow-Up Study that examined the association of baseline adiponectin levels with the primary outcome of the incidence of fatal and nonfatal coronary heart disease over a total duration of 6 years [6]. In this study, higher adiponectin levels showed associations with higher HDL cholesterol levels and lower triglyceride, C-reactive protein, HbA1c, and BMI levels. In multivariable analyses, adiponectin was inversely associated with the risk of myocardial infarction, such that the highest quintile of adiponectin demonstrated a RR of 0.56 (95% CI) 0.32–0.99. Adiponectin was therefore observed to be favorably associated with cardiovascular risk factors and decreased risk of fatal and nonfatal coronary disease.

Non-dialysis-Dependent Chronic Kidney Disease

Multiple observational studies have shown that adiponectin levels are increased in patients with kidney disease and that the degree of adiponectin elevation corresponds to the extent of renal dys-

function (Table 20.2). In the NDD-CKD population, it is currently unclear whether adiponectin serves as a cardiovascular protective agent or as an indicator of increased mortality risk.

An early prospective study conducted by Becker et al. examined a population of 227 non-diabetic patients with NDD-CKD (average GFR 63 ml/min/1.73m^2) [41]. Baseline adiponectin, insulin, and insulin resistance were measured, and patients had a follow-up period that averaged 54 months. Despite the varying stages of CKD, mean baseline adiponectin levels in this population did not show any statistically significant differences according to CKD status (6.6 ± 2.8 μg/ml vs. 6.1 ± 4.2 μg/ml for controls vs. CKD patients, respectively). However, higher fasting insulin levels and greater insulin resistance were observed in the CKD group as compared with age, sex, and BMI-matched controls. Ten patients during the follow-up period experienced non-cardiovascular events; these patients were noted to have lower adiponectin levels at baseline compared to patients who did not experience cardiovascular events (3.0 ± 1.3 vs. 6.5 ± 4.5 μg/ml, respectively). In addition, they were noted to have increased fasting insulin and serum glucose levels, as well as greater insulin resistance. This study suggests that in NDD-CKD patients, adiponectin serves as a vasoprotective agent and that hypoadiponectinemia may be a cardiovascular risk factor.

The hypothesis that adiponectin may serve a cardioprotective role in CKD has been further supported by subsequent studies. Included among these studies is a prospective analysis by Imawashi et al. that followed a group of 150 Japanese NDD-CKD patients with the goal of determining adiponectin's association with cardiovascular morbidity and mortality, including death secondary to cardiovascular disease [7]. Unlike the Becker et al. study, patients with diabetes and diabetic nephropathy were included in this trial. Baseline adiponectin levels were directly linked with increasing CKD stage. During an average follow-up period over 31.9 ± 1.5 months, patients who developed de novo cardiovascular events, including cardiovascular death, were noted to have lower adiponectin levels at baseline as compared with those who did not (5.0 ± 1.3 vs. 8.4 ± 0.7 μg/ml, respectively). Recurrent ischemic heart disease was also noted to be associated with lower adiponectin levels. When adjusted for pre-existing ischemic heart disease, smoking, and CKD stage, each 1 μg/ml increment in adiponectin level was associated with a HR of 0.86 (95% CI) 0.75–0.96; p = 0.004) for cardiovascular events and mortality. Therefore, the authors concluded that higher adiponectin levels may have a cardioprotective function independent of the elevations ensuing from kidney dysfunction.

Not all studies have corroborated a cardioprotective role of adiponectin; however, Jorsal et al. studied a cohort of 438 patients with type 1 diabetes mellitus with NDD diabetic nephropathy as defined by the presence of macroalbuminuria [25]. This group had a mean ± SD eGFR of 66 ± 28 ml/min/1.73 m^2. They were followed for an average of 8.1 years and matched with 440 patients with type 1 diabetes without macroalbuminuria. Baseline characteristics showed that patients with diabetic nephropathy had higher adiponectin levels compared to those without nephropathy. Upon follow-up, it was observed that baseline adiponectin levels were an independent predictor of all-cause mortality when adjusted for covariates that included age, sex, presence of nephropathy, blood pressure, HbA1c, creatinine, cholesterol, and antihypertensive treatment. Associations with fatal and nonfatal cardiovascular events did not reach statistical significance. In addition, adjusted analyses showed that baseline adiponectin levels predicted progression to ESRD with a HR of 2.72 (95% CI) 1.27–5.84; p = 0.10.

Menon et al. conducted a secondary analysis of the Modification of Diet in Renal Disease (MDRD) study to examine the association of adiponectin with cardiovascular outcomes and mortality risk [8]. Unlike the aforementioned studies which largely focused upon stage 1–2 CKD patients, this study focused on 820 patients with stage 3–4 CKD (mean ± SD eGFR of the cohort

was 33 ± 12 ml/min/1.73m^2) with an average follow-up of 10 years. Results of fully adjusted Cox regression models showed that each 1 μg/ml increase in adiponectin was associated with a 3% higher risk of all-cause mortality after adjustment for cardiovascular risk factors: HR 1.03 (95% CI) 1.00–1.07; $p = 0.05$. Adiponectin was also found to be associated with higher cardiovascular mortality: HR 1.07 (95% CI) 1.03–1.11; $p = 0.001$.

Dialysis-Dependent End-Stage Renal Disease

Serum adiponectin level has been observed to be approximately 2.5-fold higher in ESRD patients than in average healthy subjects [10]. Among studies of ESRD patients, the evidence is mixed with respect to associations of adiponectin with mortality risk (Table 20.2). However, multiple studies suggest that higher adiponectin levels may have a protective role in this population.

In one of the seminal studies conducted to date, Zoccali et al. conducted a prospective study following 227 Caucasian ESRD patients on hemodialysis who had no symptoms of heart failure with a mean ± SD follow-up of 31 ± 13 months. Adiponectin levels were collected at baseline, and the primary endpoints of the study were cardiovascular events and all-cause mortality risk. Baseline adiponectin levels were found to directly correlate with HDL while inversely correlating with triglyceride, insulin, and BMI levels. Results showed that the lowest tertile of adiponectin was associated with higher risk of adverse cardiovascular events (ref: highest tertile): RR 1.56 (95% CI) 1.12–1.99. After adjustment for Framingham cardiovascular risk factors, C-reactive protein, homocysteine, as well as hemoglobin, albumin, calcium, phosphate, and duration of hemodialysis, each 1 μg/mL increment in adiponectin level was associated with a 3% reduction in fatal and nonfatal cardiovascular events: HR 0.97 (95% CI) 0.93–0.99; $p = 0.04$. Hence, this study suggested a cardioprotective role for adiponectin in ESRD patients.

Subsequent studies have suggested that adiponectin's relationship with mortality may be dependent upon obesity status. In a prospective cohort study of 537 hemodialysis patients, Zoccali et al. examined whether the association between adiponectin and mortality is modified by waist circumference (WC) as a proxy of visceral body fat [42]. Investigators observed that WC negatively correlated with C-reactive protein. In survival analyses, higher adiponectin levels were associated with lower all-cause mortality among patients in the lowest tertile of WC but were associated with higher mortality among patients in the highest tertile of WC.

There have been numerous corollary studies following the trial conducted by Zoccali et al. For example, Takemoto et al. conducted a prospective cohort study of 68 Japanese hemodialysis patients [12]. This trial was distinguished by an exceptionally long follow-up period of 8 years following measurement of baseline adiponectin levels. Primary outcomes included coronary heart disease as defined by angina pectoris and fatal or nonfatal myocardial infarction. Baseline adiponectin levels were much higher in females than in male patients (15.70 ± 7.10 vs. 9.34 ± 4.28 μg/mL, respectively). Data analyses showed that plasma adiponectin was positively correlated with serum HDL cholesterol levels ($R = 0.043$; $p = 0.009$) and inversely correlated with waist circumference ($R = -0.48$; $p = 0.002$) and serum creatinine ($R = -0.39$; $p = 0.02$) which were independent parameters that influence plasma adiponectin concentrations. In Cox regression analyses, higher plasma adiponectin levels were associated with lower risk of coronary heart disease: HR 0.74 (95% CI) 0.57–0.97 in men and HR 0.79 (95% CI) 0.67–0.94 in women. However, significant associations were not observed with all-cause mortality: HR 1.03 (95% CK) 0.91–1.17 in men and HR 0.98 (95% CI) 0.91–1.06 in women.

Diez et al. conducted a retrospective study of 164 hemodialysis and peritoneal dialysis patients that examined longitudinal adiponectin levels collected at baseline and 12 months with a mean ± SD follow-up of 33.9 ± 15.7 months [11]. Results showed that compared to peritoneal dialysis patients, those receiving hemodialysis had

lower baseline adiponectin levels. In multivariate adjusted Cox regression analyses, baseline, 1 year, and mean adiponectin levels were shown to be associated with lower all-cause mortality risk. The same pattern of findings was observed for cardiovascular mortality and nonfatal cardiovascular events. However, these associations did not persist when restricted to hemodialysis patients only.

However, not all studies have corroborated a potential cardioprotective role of adiponectin. Drechsler et al. examined the data from 1255 participants from the German *Die Deutsche Diabetes Dialyse* (4D) study who underwent baseline and 6-month adiponectin measurements [14]. Primary endpoints included sudden death, stroke, myocardial infarction, combined cardiovascular events, and all-cause mortality. In crude analyses, baseline adiponectin levels were associated with higher risk of sudden death, stroke, and combined cardiovascular events (HRs 1.26, 1.40, and 1.66, respectively). However, in multivariate analyses, associations with stroke did not persist, and baseline adiponectin was associated with a higher risk of combined cardiovascular events (HR 1.27 [95% CI] 1.05–1.52) and sudden death (HR 1.39 [95% CI] 1.02–1.89). Baseline adiponectin levels were not associated with higher risk of all-cause death risk in crude or multivariate analyses. The highest tertile of baseline adiponectin levels were associated with higher incidence of cardiovascular events and stroke (HR 1.33 [95% CI] 1.03–1.72 and HR 2.39 [95% CI] 1.28–4.48, respectively). No associations were observed between the highest tertile of adiponectin and all-cause death. Rising adiponectin levels defined as an increase of levels 12.3% above baseline were associated with higher risk of adverse events. Increasing adiponectin levels showed positive correlations with rise in NT-pro-BNP and inverse correlations with change in BMI. In crude analyses, patients with rising adiponectin levels were observed to have higher rates of sudden death, myocardial infarction, and all-cause mortality: HR 1.51 (95% CI) 1.02–2.25, HR 1.66 (95% CI) 1.15–2.39, and HR 1.29 (95% CI) 1.06–1.57, respectively. However, these associations did not persist after multivariate adjustment.

Rao et al. conducted a secondary analysis of 182 hemodialysis-dependent patients from the HEMO study that measured baseline and yearly adiponectin levels over an average of 3.96 years of follow-up [15]. The primary outcome was defined as all-cause mortality, and secondary outcomes consisted of first hospitalization for cardiac causes and death from cardiac causes. Higher adiponectin levels were found to be associated with a lower risk for vascular disease with ORs of 0.70 (95% CI) 0.51–0.95. The relationship between baseline plasma adiponectin and all-cause mortality as well as cardiovascular hospitalization risk was nonlinear and best described with a quadratic transformation, but even this did not reach statistical significance. In unadjusted Cox analyses, changes in adiponectin levels from baseline did not show a statistically significant association with all-cause mortality nor cardiovascular disease outcomes. Upon adjustment for covariates which included C-reactive protein and IL-6, statistically significant associations were observed. However, subsequent adjustment for various covariates showed mixed findings, with unclear conclusions drawn from these analyses.

Kidney Transplantation Recipients

ESRD patients who undergo kidney transplantation have been observed to have lower serum adiponectin levels compared to pretransplant patients but remain higher relative to that of non-ESRD populations [43, 44]. With respect to outcomes in this population (Table 20.2), Alam et al. examined 987 Hungarian ESRD patients who underwent kidney transplantation and were followed for median duration of 51 months with a primary outcome of all-cause mortality and graft failure [16]. This study showed that adiponectin was independently associated with all-cause mortality with a HR of 1.44 (95% CI) 1.13–1.85. Compared to those in the lowest tertile, patients in the high-

est tertile of baseline adiponectin levels had an adjusted mortality HR of 1.80 (95% CI) 1.09–2.96. In addition, higher adiponectin levels were predictive of graft failure with a HR of 1.83 (95% CI) 1.48–2.26, but these associations became nonsignificant in fully adjusted models.

Leptin

Leptin is a 16-kDa adipocytokine composed of a 167-amino-acid protein that is expressed primarily by adipose tissue. It functions via receptors in the hypothalamus and regulates neuroendocrine functions, energy intake, and inflammation [45]. Leptin has a broad and important role in regulating the physiology of energy metabolism, inflammatory response, and energy storage [46–48]. It is known that leptin levels directly correlate with BMI and body fat composition and are inversely associated with malnutrition markers [49–51]. In the general population, leptin has been associated with higher risk of cerebral vascular disease, carotid intimal hyperplasia, and cardiovascular disease and is thought to be potently pro-atherogenic and pro-inflammatory [52–55]. Notably, in comparison with the general population, ESRD patients have been found to have significantly higher leptin levels, and this is hypothesized to be a result of increased production rather than decreased renal clearance [56].

Leptin, Cardiovascular Disease, and Mortality

There are very few studies which have investigated leptin's association with cardiovascular risk and mortality in the ESRD population, although small prospective and cross-sectional analyses have suggested a potentially cardioprotective role for leptin (Table 20.3). A small prospective observational study in a cohort of 53 Chinese hemodialysis patients has shown that leptin levels above the median value were associated with lower cardiovascular and all-cause mortality [59]. However, small cross-sectional studies have failed to show an association between leptin and vascular disease [58], left ventricular hypertrophy [62], and anemia [60] in the ESRD population. Further investigations are necessary to elucidate the role in leptin in the ESRD population.

Conclusion

Adiponectin and leptin are important adipokines that act on multiple organ systems. Serum adiponectin levels are strongly affected by obesity and insulin sensitivity. In studies of the general population, higher serum adiponectin levels have been suggested to have cardioprotective functions, whereas lower levels have been associated with higher risk of morbidity. In patients with kidney dysfunction, higher levels of adiponectin have been observed. However, the impact of higher adiponectin levels upon the cardiovascular morbidity and mortality of NDD-CKD and ESRD populations remains in dispute. It is unclear if higher adiponectin levels are a marker of the inflammatory state in ESRD or rather reflect general nutritional deficiency rather than a physiological response to renal failure. In the general population, high leptin levels are associated with pro-inflammatory and atherogenic responses, as well as a higher risk of cardiovascular disease. However, these associations have not been observed in the ESRD population, and small studies suggest high leptin levels may be associated with improved cardiovascular outcome. Further trials are needed to categorically qualify the role of adiponectin and leptin upon the cardiovascular health and survival of kidney disease patients.

Table 20.3 Studies of leptin, cardiovascular risk factors, cardiovascular disease, and survival in dialysis populations

Study	Study population	Study type	*N*	Age	Follow-up time	Primary outcome	All-cause mortality HR (95% CI)	CVD mortality HR (95% CI)	Conclusion
Diez et al. [57]	ESRD on PD and HD	Cross-sectional	82 (38 HD)	54.4	–	Association with vascular disease	–	–	No association between leptin and vascular disease
Diez et al. [58]	ESRD on HD	Prospective observational	118	65.1	24.7 mos	Association with CVD and all-cause mortality	No association	No association	No association between leptin and leptin/BMI ratio with CVD or all-cause mortality
Bian et al. [59]	ESRD on HD	Prospective observational	53	66	5 yrs	Association with all-cause mortality	HR 0.21 (0.06 to 0.72)	–	Low leptin associated with increased all-cause mortality
Nasri et al. [60]	ESRD on HD	Cross-sectional	36	47	–	Association with hemoglobin	–	–	Serum leptin correlated with hemoglobin; serum leptin correlated with BMI
Nasri et al. [60]	ESRD on HD	Cross-sectional	41	46	–	Association with left ventricular hypertrophy	–	–	No association between serum leptin and left ventricular hypertrophy
Park et al. [61]	ESRD on PD	Prospective observational	131	50.8	5 years	Association with all-cause mortality	Higher L/A RR 1.17 (1.07–1.27) for all-cause mortality	–	Higher leptin, lower ADPN, and higher L/A associated with increased risk of mortality

Abbreviations: *CVD* cardiovascular disease, *ESRD* end-stage renal disease, *PD* peritoneal dialysis, *HD* hemodialysis, *ADPN* adiponectin, *L/A* leptin to adiponectin ratio

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