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# Understanding Adiponectin Dynamics in Chronic Kidney Disease

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## ABSTRACT

Adiponectin is an adipokine known for its insulin-sensitising effects, including the suppression of hepatic gluconeogenesis, enhancement of fatty acid oxidation, and promotion of glucose uptake. Within the kidneys, adiponectin is primarily localised to the arterial endothelium, smooth muscle cells, and capillary endothelium. Adiponectin might be considered a marker of many negative factors in chronic kidney disease. The last few years have yielded a growing body of evidence that adiponectin is a multifunctional protein with anti-inflammatory, metabolic, anti-atherogenic, and reactive oxygen species (ROS)- protective actions. In recent years, accumulating evidence has highlighted adiponectin as a multifunctional protein with anti-inflammatory, metabolic, anti-atherogenic, and antioxidant (ROS-protective) properties. Moreover, adiponectin appears to exert a range of beneficial and direct effects on various renal cell types and kidney pathologies. Similarly, adiponectin has demonstrated numerous positive and direct actions in kidney diseases, as well as across multiple kidney cells. Data from extensive cross-sectional and cohort studies have shown a positive correlation between serum adiponectin levels and mortality in patients with chronic kidney disease.

This suggests a complex interaction between local adiponectin action, comorbidities, and uremic milieu. In this review, we explore the multifaceted role of adiponectin in chronic kidney disease, examining its physiological functions, pathological implications, and potential as a biomarker or therapeutic target.

**Keywords:** Adiponectin, Biomarker, Comorbidities

**Abbreviations:** CKD- chronic kidney disease, EGRF- estimated glomerular filtration rate

## INTRODUCTION

Adiponectin has been identified as a vital regulator of glucose and lipid metabolism since its discovery. Further research confirmed its “anti-inflammatory or anti-apoptotic properties on human cells. It is primarily composed of adipocytes. With 244 amino acids (30 kDa), the human adiponectin protein has a complex primary structure that includes a globular domain, a collagenous domain with 22 G-X-Y repeats, a signal peptide, and a highly variable region. Three distinct structural forms trimer LMW (low molecular weight), hexamer MMW (middle

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molecular weight), or 12–18-mer HMW (high molecular weight)" are found in significant amounts in human serum. **(Combs et.al,2001)**

Globular adiponectin is another active form that circulates in the body. It has biological activity in humans and is produced by the "proteolytic cleavage of full-length adiponectin. The concentration of adiponectin varies by gender, with higher levels seen in females. T-cadherin, adiponectin receptor 1 (AdipoR1), or adiponectin receptor 2 (AdipoR2) are three known receptors for adiponectin that have been found. The structure of the 1st two receptors is similar, with seven transmembrane domains and an intracellular zinc-binding motif that could cause further signalling in the cell**. (Tanabe et.al,2015)**

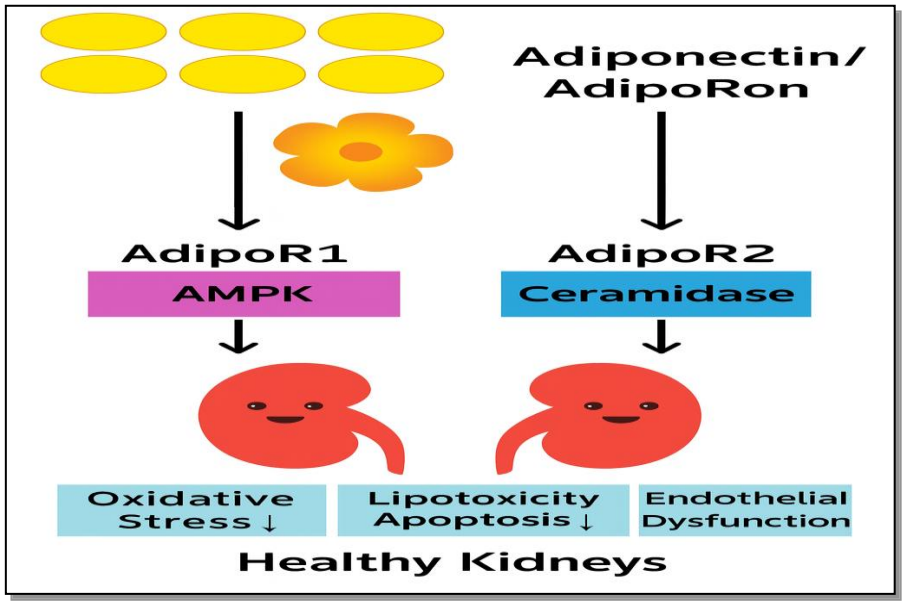


**Figure:1** Adiponectin activates AdipoR1 and AdipoR2 pathways, reducing oxidative stress, lipotoxicity, apoptosis, and endothelial dysfunction to maintain kidney health.

**Adiponectin action in the kidney**

The liver is the primary producer of adiponectin, which is thought to have a supporting role in renal clearance physiology (Hopf et.al2009). Due to its enormous molecular weight (28 kDa), only adiponectin monomers or dimers can get through the urine and the glomerular filtration barrier (**Kim, Y et.al,2019**). The endothelium of the kidney's arteries, smooth muscle cells, brush border epithelial cells of the proximal or distal tubules, or capillary endothelium, to a lesser degree, are the primary sources of adiponectin. Adiponectin is also produced by proximal tubular cells, mostly in response to inflammation. **(Christou et.al2014).**

Bowman's capsule epithelium, mesangial cells, podocytes, or endothelial cells all have adiponectin receptors within glomeruli. Additionally, proximal tubular cells include them. AdipoR1 is present in many of these receptors. AdipoR1 mRNA is expressed in human proximal tubular cells at a level 20 times greater than that of AdipoR2 (**Perri et.al,2013**).

The secretion of adiponectin from adipose tissue remained relatively unchanged. No substantial difference was observed among the isoforms. Injection of plasma from mice with

nephrectomies vs mice with normal renal function similarly slowed adiponectin clearance. Adiponectin function is inhibited by the toxin known as cystatin C. **(Smith et.al,2022).**

Recent studies indicate specific ceramidase activity associated with the intracellular component of such receptors. AdipoR1 occurs mainly in human cells, particularly in skeletal muscle, while AdipoR2 is primarily located in the human liver. **(Vasiliauskaitė-Brooks et.al,2017).**

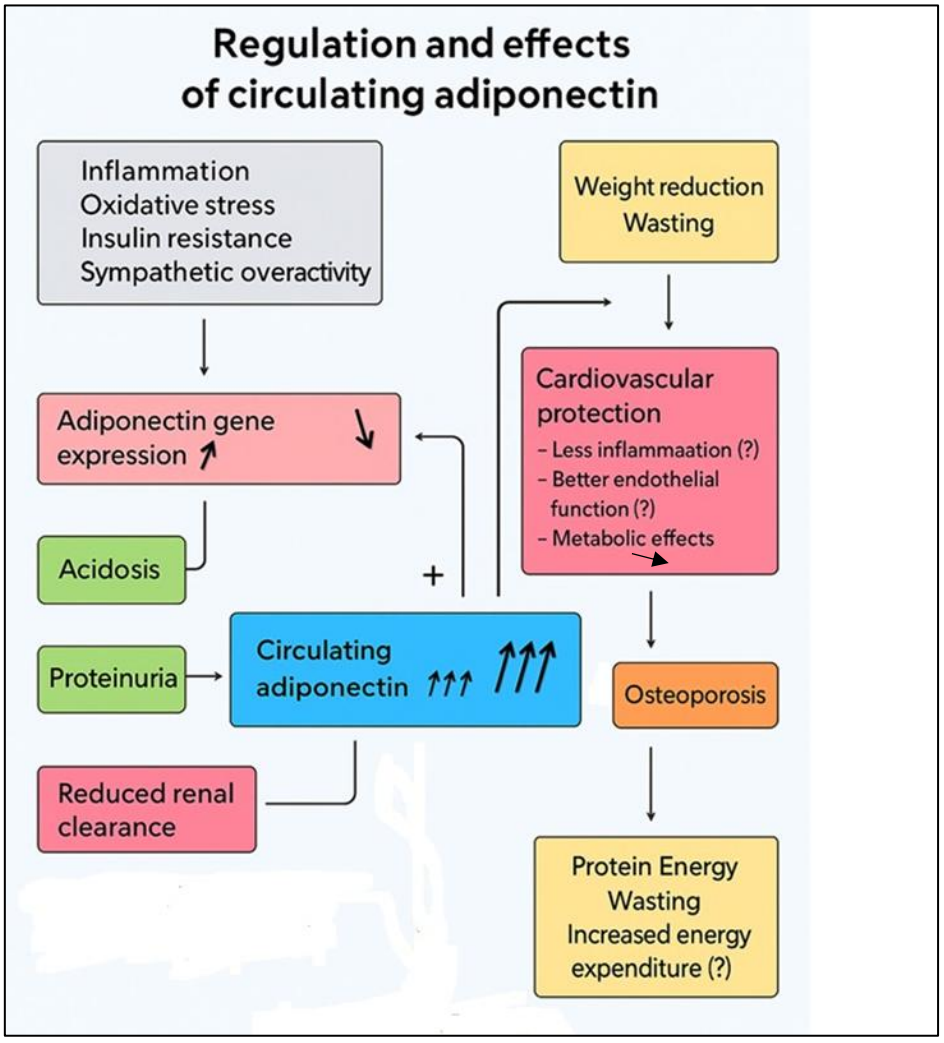


**Figure:2** Determinants and consequences of circulating adiponectin in kidney disease

**Adiponectin in Chronic Kidney Disease**

Several studies conducted over the past 20 years have demonstrated the growing significance of adiponectin in kidney disease. In this demographic, cardiovascular disease (CVD) continues to be the leading cause of morbidity. Chronic inflammation, atherosclerosis, Malnutrition, and increased oxidative stress are other impacts. Patients with ESRD (end-stage renal disease) have serum adiponectin receptors that are 2 times higher than those of persons with normal kidney function, even though they have a negative metabolic state. Adipose tissue secretes more adiponectin, which contributes to this. Patients receiving hemodialysis or peritoneal dialysis have serum adiponectin levels approximately three times higher than those in the normal

population, and neither treatment significantly decreases adiponectin levels. (**Martinez Cantarin et.al,2014).**

Studies have shown that oxidative stress or sympathetic nerve activity are present in chronic kidney disease (CKD), and are variables that contribute to decreased adiponectin secretion. Additionally, a negative relationship exists between plasma concentration, adiponectin production, and visceral fat. Additionally, Nagakawa et al. discovered a negative correlation between plasma adiponectin and the quantity of metabolic syndrome components. (**Kim, et al. 2016)**

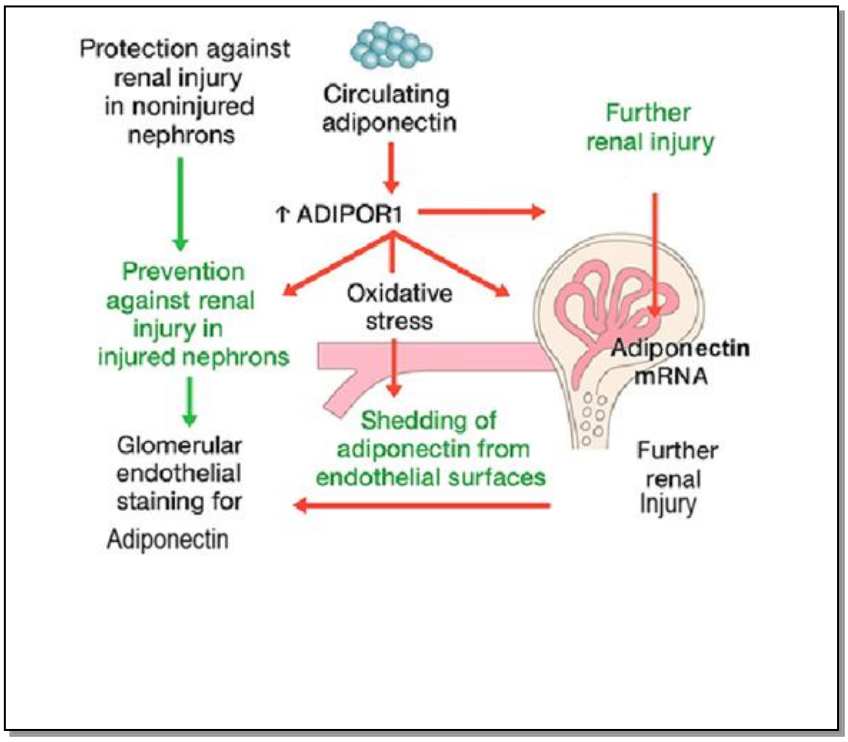


**Figure:3** Dual role of adiponectin in renal protection and injury

Additionally, diabetic nephropathy causes "a significant increase in serum adiponectin levels, especially in those with advanced stages of the disorder and A3 albuminuria. The HMW form of adiponectin, whose concentration has a negative correlation with EGFR (estimated glomerular filtration rate), is increased chiefly because of this. An independent risk factor for the severity of diabetic nephropathy is higher levels of adiponectin. Diabetic rat kidneys in animal models have demonstrated decreased AdipoR density and function; however, the findings have not been consistent, particularly in the case of AdipoR2, and require further discussion. (**Christou, G.A. et.al, 2014)**

**Adiponectin as a Marker of Kidney Disease**

Adiponectin may serve as a marker for kidney damage and suggest that the disorder may develop.

According to **Kollerits et al**., higher serum adiponectin may predict the progression of CKD in men but not in women. Patients with type 1 diabetes (T1D) have shown a similar relationship between baseline blood adiponectin and the progression of CKD. However, in prospective

cohort research of older Japanese people without CKD, serum adiponectin and its HMW isoform have not been related to a reduction in eGFR. It's interesting to note that in this research group, serum adiponectin is inversely correlated with knee extension strength and hand grip. The value of adiponectin as a urine marker of kidney injury has been examined in novel experiments. Significantly more LMW or HMW forms were eliminated in the urine of patients with proteinuria greater than 150 mg/dL. In proximal tubular cells, adiponectin in these forms can activate AdipoR1, resulting in an anti-inflammatory effect. According to one study, children with systemic lupus erythematosus may have kidney damage that can be predicted by urinary levels of osteopontin and adiponectin. The authors discovered that worse biopsy NIH-CI (chronicity index) scores and observed EGFR declines were associated with higher amounts of these markers. Higher levels of these biomarkers, however, predicted chronic disorder with a moderate degree of accuracy (AUC = 0.75), and the observations were limited to a single year.

Many authors established an ultrasensitive enzyme-linked immunosorbent test that can detect remarkably low quantities of urine adiponectin. The findings indicated a markedly elevated urine adiponectin content in individuals with diabetes. Additionally, a positive connection has been observed between urine adiponectin levels and the progression of CKD. Furthermore, western blot analysis revealed that, in contrast to healthy controls, diabetic patients excreted MMW or even HMW adiponectin in their urine. researchers proposed that testing urinary adiponectin levels, specifically the MMW variant, may be more dependable than evaluating the albumin-to-creatinine ratio (ACR).

Several trials have evaluated urine adiponectin in non-diabetic individuals. One of them observed that in patients with hypertension receiving olmesartan, a blocker of the angiotensin II receptor AT1, albuminuria and urine adiponectin levels were positively correlated. (**Nishimura, M. et.al,2013)**

**The Beneficial Role of Adiponectin:**

Recent years have yielded increasing evidence that adiponectin is a multifunctional protein, exhibiting anti-atherogenic properties, as well as metabolic, anti-inflammatory, and protective effects against reactive oxygen species. The discoveries, derived from several investigations primarily involving animals or cell lines, have prompted the exploration of new therapeutics for medical problems encompassing atherosclerosis, diabetes, and obesity. Adiponectin has been shown to have numerous beneficial and direct effects in renal disorders and various renal cells. However, results from several cross-sectional and cohort studies indicated a significant connection between serum adiponectin levels and death in CKD. The true nature of this adiponectin paradox remains uncertain. Several researchers propose that elevations in adiponectin may be directly caused by reduced renal clearance or may serve as a compensatory mechanism in response to the increasing insults associated with deterioration in renal function. Yet, some well-designed studies have demonstrated an independent association between adiponectin and death. Adiponectin has been closely associated with PEW, natriuretic peptides, and, in certain studies, vascular calcifications, all of which are distinct risk factors for death in patients with CKD. The link between adiponectin and these problems remains unclear. (**Ouchi, N et.al,2011**).

**Table1: Role of Adiponectin in Chronic Kidney Disease (CKD)**

| Influencing Factors | Adiponectin in CKD | Outcomes / Associations |
|---|---|---|
| **Fluid overload & Natriuretic peptides** | ↑Adiponectin | Contributes to altered metabolic state |
| **Protein energy wasting (indicator)** | ↑ Adiponectin | May drive or indicate wasting process |
| **Adiponectin resistance** | Reduced effectiveness of adiponectin despite higher levels | Diminished protective effects |
| **Mineral & bone disorder** | Related to altered adiponectin signaling | • Bone loss<br>• Reduction of renal Klotho<br>• Possible vascular calcification |
| **Anemia** | Linked with adiponectin imbalance | Worsening CKD outcomes |
| **Protective effects (potential roles)** | Adiponectin may act beneficially | Anti-inflammatory<br>Anti-atherogenic<br>Endothelium protection<br>Insulin sensitization<br>Podocyte protection |

Adiponectin may serve as an indicator of various negative aspects in CKD; however, recent studies have discovered its significant role in mineral or bone metabolism, as well as vascular calcifications. Adiponectin is also crucial for metabolism, although its relationship to malnutrition remains unclear. Many of those traits resulted in varying outcomes, and the potential for adiponectin receptor agonist treatment requires additional research.

**Trials of Adeponectin:**

A cohort of patients with CKD stages 3–4 was studied by **Menon et al. (2006);** the mean age was 52±12 years, the mean GFR was 33±12 ml/min/1.73 m², and the mean adiponectin levels were 12.8±8.0 µg/mL. Ten per cent of the cohort were current smokers, 60% were men, and 85% were white. A favourable cardiovascular risk profile, which includes a reduced BMI, triglycerides, and CRP, along with higher HDL cholesterol, has been associated with higher adiponectin levels. Individuals in the highest adiponectin tertile also had lower levels of insulin,

glucose, HbA1c, and HOMA, as well as a reduced prevalence of diabetes. However, paradoxically, higher adiponectin levels have also been linked to a greater risk of CKD, as indicated by increased proteinuria and decreased GFR. Significantly, elevated adiponectin predicted higher all-cause and cardiovascular deaths in this CKD population. Authors emphasised that these findings do not contradict the cardioprotective role of adiponectin seen in the general population, but rather highlight the distinct pathophysiological profile of CKD patients, suggesting the need for further research into underlying mechanisms.

**Rhee et al. (2015)** investigated 501 hemodialysis (HD) patients, among whom 50 deaths occurred over 631.1 person-years of follow-up. Their analysis discovered that patients in the highest adiponectin tertile had significantly increased death compared to those in the lowest tertile, with hazard ratios around 3.3 even after adjusting for body composition and lipid levels. These associations remained robust across various models, indicating that high adiponectin levels are independently associated with increased mortality in patients with HD. The study calls for further investigation to understand the biological basis of this relationship and to explore potential therapeutic targets.

**Abdallah et al. (2012)** found that plasma adiponectin levels were significantly elevated in HD patients, averaging 18.1 ± 6.8 µg/mL, nearly three times higher than in healthy individuals (6.2 ± 1.8 µg/mL). Most HD patients (63.2%) had adiponectin levels above the normal range. Female patients had significantly higher levels than males, a pattern that persisted even after adjusting for BMI and was also observed in healthy controls. Interestingly, patients who experienced new cardiovascular events had significantly lower adiponectin levels (13.9 ± 6.4 µg/mL) compared to those who remained event-free (18.6 ± 8.4 µg/mL). Risk of cardiovascular events was nearly doubled in patients with adiponectin levels below 15.1 µg/mL. These results support a protective role for adiponectin in cardiovascular outcomes among HD patients, presenting a contrasting perspective to some other findings.

**Moreno et al. (2016)** conducted a large-scale study in diabetic populations and found a paradoxical association between adiponectin and all-cause death. For each standard deviation increase in adiponectin, hazard ratios ranged from 1.30 to 1.43 across different study cohorts. These associations remained significant after adjusting for demographics, adiposity, kidney function, diabetes-related factors, and medications. Notably, the relationship between adiponectin and death was only present in individuals with preserved kidney function (GFR≥60 ml/min/1.73m²), but not in those with reduced GFR. This strong interaction between adiponectin and kidney function suggests a complex, context-dependent role of adiponectin in mortality risk, particularly among patients with type 2 diabetes.

**Kim et al. (2018)** studied CKD patients with a mean age of 53.6 ± 12.2 years or a mean eGFR of 50.4 ± 30.2 mL/min/1.73 m². Adiponectin levels have been significantly correlated with BMI, eGFR, CRP, and haemoglobin, and are positively associated with HDL cholesterol, the comorbidity index, and proteinuria. In a multivariable analysis, higher adiponectin levels were independently associated with lower haemoglobin levels in both men and women. Among patients who were not anaemic at baseline, those with higher adiponectin had a significantly increased risk of developing anaemia during follow-up. Each 1 µg/mL increase in adiponectin was associated with 2% increased risk of incident anaemia. Such results show that adiponectin

might play a role in the development of anaemia in CKD patients, further highlighting its complex biological effects in the context of kidney disease.

**Hyun et al. (2017)** conducted research involving 1,303 predialysis CKD patients, identifying that 72 individuals (5.5%) exhibited protein-energy wasting (PEW). "Multivariate logistic regression analysis illustrates that higher adiponectin levels have been significantly associated with the presence of PEW, with an odds ratio of 1.04 per 1µg/mL increase (95% CI: 1.01-1.08). Patients in the highest adiponectin quartile had a markedly increased likelihood of PEW compared to those in the lowest quartile (odds ratio: 10.54; 95% CI: 1.28-86.74). Furthermore, in a multiple linear regression analysis focused on PEW indicators, adiponectin has been most strongly linked to urinary creatinine excretion (UCE), a surrogate marker of muscle mass ($\beta$ = -2.21; 95% CI: -4.13 to -0.28; $R^2$ = 0.67). These outcomes suggest that elevated serum adiponectin is associated with PEW in CKD, particularly reflecting reduced muscle mass.

**Nomura-Nakayama et al. (2018)** explored the relationship between adiponectin fractions and vascular calcification in Japanese renal allograft recipients over eight years. They analysed changes in the aortic calcification area index (ACAI) by quartiles. They found that patients with persistently elevated high-molecular-weight adiponectin (HMW-ADPN) experienced significantly lower progression in ACAI. Multiple regression analysis illustrated that increased ACAI has been associated with older age at transplantation and a history of cardiovascular complications. At the same time, higher HMW-ADPN concentrations have been linked to improvements in ACAI. Serum HDL-C also emerged as a positive contributor to higher HMW-ADPN levels. Immunohistochemical analysis revealed adiponectin localised to CD31-positive arterial endothelial cells in kidney allografts and showed co-localisation with T-cadherin and AdipoR1, with only partial overlap with AdipoR2. These results suggest that, via improving adiponectin binding to vascular endothelial cells via T-cadherin or adiponectin receptors, HMW-ADPN and HDL-C may both prevent vascular calcification.

**Okuno et al. (2012)** investigated the role of adiponectin in bone metabolism among male patients undergoing hemodialysis. The research identified significant negative relationships among "serum adiponectin and bone mineral density (BMD) at 1/3 distal radius ($r$ = -0.229, $p$=0.014), ultra-distal radius ($r$ = -0.286, $p$=0.002), and lumbar spine ($r$ = -0.227, $p$=0.013). Multiple linear regression analyses established that serum adiponectin is independently associated with BMD at 1/3 distal radius and ultra-distal radius, even after controlling for age, dialysis duration, body weight, fat mass percentage, and intact PTH levels. However, no significant association was found with lumbar spine BMD and the variable. Additionally, a positive correlation has been observed between serum adiponectin and serum NTX, a marker of bone resorption ($r$ = 0.321, $p < 0.001$). However, no significant correlation has been found with" bone alkaline phosphatase (BAP). The study concludes that elevated adiponectin levels are associated with lower BMD and may contribute to mineral and bone disorders in CKD stage 5D patients through enhanced bone resorption.

**Rao et al. (2008)** reported that baseline plasma adiponectin levels in CKD patients were approximately double those observed in the general population. These levels showed an inverse correlation with log-transformed CRP and BMI, indicating a relationship between higher adiponectin and lower inflammation and adiposity. Over time, adiponectin levels increased by

an average of 0.95µg/mL (95% CI: 0.12-1.78µg/mL; P=0.03), while this trend lost significance after adjusting for covariates. Notably, patients with pre-existing cardiovascular disease had lower baseline adiponectin levels (adjusted odds ratio, 0.67; P = 0.03). Adiponectin levels were predictive of all-cause death and the combined outcome of cardiovascular events and death, with statistical significance (P<0.01). Furthermore, levels measured longitudinally continued to predict adverse outcomes. The association between adiponectin and these outcomes followed a non-linear (quadratic) pattern, with increased hazards at both low and high extremes of adiponectin concentrations. These associations were strengthened after adjusting for factors like serum albumin, existing cardiovascular disease, and dialysis parameters. In summary, low adiponectin was associated with inflammation and cardiovascular disease at baseline. In contrast, both low and high levels have been predictive of increased death and cardiovascular risk, highlighting a complex and potentially U-shaped risk relationship.

**Kim et al. (2017)** investigated the relationship between serum adiponectin levels and vascular stiffness in patients with CKD. Research has indicated that elevated quartiles of serum adiponectin are predominantly noted in women and are correlated with decreased eGFR, reduced body mass index (BMI), or increased urinary albumin-to-creatinine ratios. Serum adiponectin concentrations exhibited a strong connection with heart–femoral pulse wave velocity (hfPWV) and mean brachial–ankle pulse wave velocity (baPWV), even after controlling for age as well as sex. In multivariable linear regression analysis, adiponectin was found to be correlated primarily with hfPWV (B=0.028; 95% CI: 0.004-0.051; P=0.020) and not with mean baPWV. Multivariate logistic regression analysis revealed a significant correlation between serum adiponectin and the highest quartile of hfPWV values, but not with baPWV. The data indicate that serum adiponectin is independently and strongly correlated with aortic stiffness, as assessed by hfPWV, in individuals with CKD, implicating adiponectin in the pathophysiology of vascular changes associated with CKD.

A systematic review and meta-analysis published in ***Metabolites*** **(2025)** included 12 studies and 2,523 CKD patients, examining the link between circulating adiponectin and all-cause death. While the overall pooled hazard ratio (HR) per 1 µg/mL increase has not been statistically significant (HR = 1.003; 95% CI: 0.981-1.025), subgroup analyses revealed essential nuances. Elevated adiponectin was linked with higher mortality in non-Asian populations, studies with fewer than 47% women participants, and in those with BMI ≥25 kg/m². Paradoxically, in patients undergoing peritoneal dialysis and in studies with ≥47% female participants, higher adiponectin levels were associated with a reduced mortality risk.

The KNOW-CKD cohort study (published earlier) involving 2,238 Korean CKD patients found that higher adiponectin levels predicted progression to adverse renal outcomes, including dialysis initiation or a doubling of serum creatinine (HR=1.39; 95% CI: 1.05-1.84, p=0.021). However, this predictive ability disappeared once baseline eGFR was adjusted for implying that adiponectin may serve more as a *marker* of pre-existing renal dysfunction rather than a direct causal factor. In contrast, a Mendelian randomisation study using genetic data found that higher adiponectin levels causally protect kidney function and reduce CKD risk. This suggests that observational studies may be biased by reverse causality or confounding. (**Wu et.al,2022).**

A 2023 Biomedicines study also demonstrated that in non-dialysis-dependent CKD patients, serum adiponectin correlated positively with better endothelial function, measured via vascular reactivity index (VRI).

## Conclusion

Adiponectin plays a multifaceted role in chronic kidney disease, extending beyond its traditional metabolic functions to include anti-inflammatory, anti-atherogenic, and antioxidant effects. Its expression in renal tissues and interactions with various kidney cell types underscore its potential significance in renal pathophysiology. However, paradoxical association among elevated serum adiponectin levels and increased death in CKD highlights the complexity of its role, likely influenced by the uremic environment, systemic inflammation, and comorbid conditions. While adiponectin holds promise as a biomarker and possibly a therapeutic target in CKD, further research is necessary to clarify its mechanisms of action, prognostic value, and potential clinical applications. Understanding this adipokine in greater depth may contribute to improved risk stratification and the development of targeted interventions in the treatment of CKD.

Adiponectin is increasingly recognised as a crucial player in the pathophysiology of CKD, with anti-inflammatory, metabolic, and renoprotective properties. Despite its potential, the observed link between high adiponectin levels and increased death in CKD suggests a complex and context-dependent role. As research progresses, adiponectin may emerge not only as a valuable biomarker but also as a potential therapeutic target. A deeper understanding of its mechanisms could open new avenues for personalised treatment strategies in CKD.

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