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Adipocytokines in renal transplant recipients

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Abstract

In the last two decades, perceptions about the role of body fat have changed. Adipocytes modulate endocrine and immune homeostasis by synthesizing hundreds of hormones, known as adipocytokines. Many studies have been investigating the influences and effects of these adipocytokines and suggest that they are modulated by the nutritional and immunologic milieu. Kidney transplant recipients (KTRs) are a unique and relevant population in which the function of adipocytokines can be examined, given their altered nutritional and immune status and subsequent dysregulation of adipocytokine metabolism. In this review, we summarize the recent findings about four specific adipocytokines and their respective roles in KTRs. We decided to evaluate the most widely described adipocytokines, including leptin, adiponectin, visfatin and resistin. Increasing evidence suggests that these adipocytokines may lead to cardiovascular events and metabolic changes in the general population and may also increase mortality and graft loss rate in KTRs. In addition, we present findings on the interrelationship between serum adipocytokine levels and nutritional and immunologic status, and mechanisms by which adipocytokines modulate morbidity and outcomes in KTRs.

Key words: adiponectin, kidney transplantation, leptin, resistin, visfatin

Introduction of adipocytokines

In healthy individuals, the role of adipocytokines on various outcomes has been widely studied. However, little is known about how impaired kidney function and renal replacement therapy modify these associations [1]. For example, few studies have examined the impact of adipocytokines on long-term outcomes, such as graft loss and death, in kidney transplant recipients (KTRs). In Table 1, we summarize all studies investigating the role of adipocytokines in KTR and chronic kidney disease (CKD) patients.

Leptin was first described as a biomarker of obesity two decades ago; it is a 16-kDa peptide product of the obese gene predominantly secreted by white adipose tissue with the primary function of modulating hunger and satiety [72, 73]. Leptin crosses the blood–brain barrier and inhibits neuropeptide Y neurons. I also activates the sympathetic neuron system in the hypothalamus and increases circulating sympathetic hormone levels [74–76]. Leptin acts upon the Ob leptin receptors and activates tyrosine kinase and intracellular pathways [72, 75].

Leptin's counterpart is adiponectin, which negatively correlates with nutritional parameters, suggesting that higher

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Table 1. Studies evaluating adipocytokines in renal transplant recipients and patients with CKD

Author (year)	Number of patients	RRT	Findings	Positive correlations	Negative correlations	Lack of correlations
(A) Leptin						
Agras *et al.* (2005) [2]	41	Tx.	Leptin seems to increase bone mass.	BMI, BMD, z score of BMD		
Agras *et al.* (2006) [3]	63	Tx.	Leptin has an effect on lymphoid stem cells.	CD34/7		CD34/7/8/4
Baczkowsk *et al.* (2000) [4]	28	Tx.	Imbalance between leptin and body weight also persists after renal transplantation			Cortisol, BMI
El Haggan *et al.* (2004) [5]	41	Tx.	Pretransplant leptin levels reduced after transplantation	Fat mass, CRP		Dietary intake
Fonseca *et al.* (2015) [6]	40	Tx.	Leptin levels are independently determined by graft function	Male, DGF		Acute rejection
Kagan *et al.* (2002) [7]	24	Tx.	Leptin shows correlation with gender, BMI, insulin and cortisol levels	Gender, BMI, cortisol, insulin		
Kayacan *et al.* (2003) [8]	34	Tx.	Pretransplant leptin levels reduced after transplantation and was not effected by alimentary intake	HOMA, fat mass		
Kokot *et al.* (1998) [9]	40	Tx	Pretransplant leptin levels reduced after transplantation	BMI	Age	
Kokot *et al.* (1999) [10]	nd.	Tx	Elevated leptin levels not only modulated by BMI	BMI		
Kovesdy *et al.* (2010) [11]	978	Tx	Leptin lowers the bone turnover independently from PTH	PTH	vitD	
Landt *et al.* (1998) [12]	29	Tx	Pretransplant leptin levels reduced after transplantation	BMI		Gender
Lee *et al.* (2010) [13]	55	Tx.	Leptin correlates with metabolic syndrome	MetSy, waistCX, BMI, fat mass, CRP		
Lee *et al.* (2014) [14]	74	Tx.	Leptin was positively associated with peripheral arterial stiffness among renal transplant recipients			
Malyszko *et al.* (2005) [15]	27	Tx.	Leptin is associated with graft function, but not related to BMD and bone metabolism	Body mass/fat, creatinine		Nutrition, BMD
Nicoletto *et al.* (2012) [16]	32	Tx.	Pretransplant leptin levels reduced after transplantation	Gender, BF, HOMA		
Rafieian-Kopaei *et al.* (2013) [17]	72	Tx	Leptin levels and duration of kidney transplant shows strong negative correlation	Gender	Duration of kidney Tx	Age, BMI, creatinine
Souza *et al.* (2007) [18]	32	Tx.	Pretransplant leptin levels reduced after transplantation	HOMA, fat mass		GFR
(B) Adiponectin						
Adamczak *et al.* (2007) [19]	228	Tx	ADPN levels are higher in RTR than in healthy controls, but lower than in HD patients		BMI, GFR, HOMA-IR	
Adamczak *et al.* (2011) [20]	88	Tx	Role of ADPN in LVH and atherosclerosis cannot be confirmed			
Alam *et al.* (2012) [21]	987	Tx	Elevated levels of ADPN increase mortality		GFR, BMI, abd.circ., CRP	CCI
Bayes *et al.* (2007) [22]	68	Tx	Atorvastatin therapy did not modulate ADPN levels	HDL	HOMA-IR, creatinin	
Bayes *et al.* (2005) [23]	199	Tx	ADPN were lower, BMI higher in patients who developed NODAT	TNF, BMI, PAPP-A	Insulin	Age, sex
Canas *et al.* (2012) [24]	157	Tx	ADPN has an inverse association with insulin resistance		HOMA-R, c-IMT	
Chitalia *et al.* (2010) [25]	43	Tx	ADPN levels do not predict the CV risk in RTR	hsCRP	GFR, BMI, Hgb, waist circumference	BP, smoking, lipids, DM
Chudek *et al.* (2003) [26]	44	HD/Tx	Kidney plays an important role in biodegradation of ADPN		HOMA-IR	
Chudek *et al.* (2013) [27]	372	Tx	ACE I/D polymorphism modulates ADPN levels	Female, ACE II genotype	BMI	
Fonseca *et al.* (2015) [6]	40	Tx	ADPN level is not only modified by early graft function	Male, DGF		Acute rejection
Ho *et al.* (2015) [28]	69	Tx	ADPN has negative correlation with arterial stiffness		DM, smoking, BMI, waist CX, BP, arterial stiffness	

Table 1. Continued

Author (year)	Number of patients	RRT	Findings	Positive correlations	Negative correlations	Lack of correlations
Idorn *et al.* (2012) [29]	57	Tx	ADPN level decreases after transplantation and does not predict NODAT		GFR, BMI, insulin	
Kaisar *et al.* (2009) [30]	137	Tx	Hypoadiponectinemia associated with CVD	HDL, female	BMI, MetSy, IGT, TG, CRP, GFR	
Kang *et al.* (2012) [31]	575	Tx	ADIPOQ rs1501299 is associated with PTDM in a sex-specific manner			
Kulshrestha *et al.* (2013) [32]	74	Tx	Patients with metabolic syndrome have lower ADPN levels after transplantation		Clinical events	
Lee *et al.* (2011) [33]	55	Tx	Body fat mass is an independent predictor of ADPN levels		Fat mass, waist CX, MetSy	
Leibowitz *et al.* (2013) [34]	35	Tx	ADPN in hypertensive patients is not a predictive factor for CVD			BMI, TG
Malyszko *et al.* (2005) [35]	82	Tx	ADPN seems to have defense mechanism against endothelial damage	CD146, thrombomodulin, creatinine	BMI, protein Z	
Nicoletto *et al.* (2013) [36]	270	Tx	TT genotype of ADPN increases the prevalence of NODAT			
Nishimura *et al.* (2009) [37]	98	Tx	TAC and ARB modulate ADPN levels and posttransplant ADPN levels correlate with NODAT		HOMA-IR	hsCRP
Prasad *et al.* (2012) [38]	129	Tx	ADPN level lower in South African population		GFR	
Roos *et al.* (2012) [39]	206	Tx	Pretransplant ADPN level predicts higher risk for graft loss		Graft loss	
Sethna *et al.* (2009) [40]	33	Tx	Lower ADPN levels associate with higher ambulatory BP		HT	
Shen *et al.* (2007) [41]	54	Tx	ADPN levels are higher in RTR than in healthy controls, but lower than in HD patients (AdipoR1/2)		HOMA-IR	
Shu *et al.* (2012) [42]	271	Tx	ADPN level is lower in patients with metabolic syndrome, even with lower GFR	HDL	GFR, MetSy, BMI	
Taherimahmoudi *et al.* (2010) [43]	67	Tx	ADPN levels are higher in RTR than in healthy controls, but lower than in HD patients. ADPN did not decrease immediately after transplantation			BMI, HOMA-R, GFR
Teplan *et al.* (2007) [44]	68	Tx	Immunosuppressive therapy could decrease BMI	Leptin	BMI	
Teplan *et al.* (2008) [45]	140	Tx	In obese RTR, ADMA is increased and ADPN levels are decreased		BMI	
Yilmaz *et al.* (2005) [46]	27	Tx	ADMA, hsCRP decreasing instantly after transplantation, not like FMD and ADPN (they change later on)			
Yu *et al.* (2011) [47]	398	Tx	SNP-45/276 of the ADPN gene were significantly associated with an increased risk for NODAT			
(C) Visfatin						
Axelsson *et al.* (2007) [48]	189	CKD	Elevated with higher CKD stages and may predict mortality	IL-6, hsCRP, VCAM	GFR	
Bessa *et al.* (2010) [49]	40	CKD	Visfatin is strongly associated with ED and flow-mediated dilatation	ICAM, VCAM, CRP, IL-6	FMD, GFR	
Carrero *et al.* (2009) [50]	246	CKD	Elevated visfatin is associated with anorexia	PEW	TG, Chol, albumin	BMI, leptin
Eleftheriadis *et al.* (2013) [51]	33	HD	Visfatin is elevated in HD patients and is connected with decreased demands for rHuEpo	TSAT, Hgb		DM, BMI, IL-6

Table continues

Table 1. Continued

Author (year)	Number of patients	RRT	Findings	Positive correlations	Negative correlations	Lack of correlations
Erten *et al.* (2008) [52]	31/30	HD/CAPD	In CAPD patients, visfatin is higher than in HD/healthy individuals	IL-6, TNF	Left ventricular diastolic function	Left ventricular mass index
Kato *et al.* (2009) [53]	68	HD	Visfatin shows a strong association with time spent on HD	Time on HD, hsCRP	Albumin	BMI, adiponectin, body fat
Lu *et al.* (2013) [54]	173	CKD	Visfatin level is significantly higher in CAD patients and correlates with E-selectin	CAD, hsCRP, BNP, WBC, LDL	GFR, albumin	
Mahmood *et al.* (2010) [55]	50	CKD	Higher than in healthy controls. No modulation by DM	Proteinuria	GFR	DM
Malyszko *et al.* (2009) [56]	100	Tx	Higher than in healthy controls	VCAM, CRP, PTH	GFR, albumin	Gender, comorbidities, medication
Malyszko *et al.* (2010) [57]	75/40	HD/CAPD	Clearance modulated by RRT type, visfatin could be the link between inflammation and adipocytokines	TG, hsCRP, IL-6, TNF, ICAM, VCAM, CD146, HD vin	GFR	
Mu *et al.* (2011) [58]	117	CKD	Visfatin may play an important role in uremia-related atherosclerosis	ED, hsCRP, TG, LDL	GFR, FMD, HDL	
Yilmaz *et al.* (2008) [59]	58	Tx	Visfatin levels decline after Tx	ED, hsCRP	GFR, FMD	Medication
Yilmaz *et al.* (2008) [60]	406	CKD	Visfatin is associated with ED independently from inflammation	ED, hsCRP	GFR, FMD	
(D) Resistin						
Akagun *et al.* (2014) [61]	69	HD	Increased in HD patients with failed renal allografts	TNF, IL-6, hsCRP	Albumin	
Chung *et al.* (2012) [62]	100	HD	Low resistin levels independently predict poor hospitalization-free survival			IL-6
Dan *et al.* (2014) [63]	96	CKD	Serum resistin is higher in the CKD population			
Filippidis *et al.* (2005) [64]	33	HD	HD does not effect the resistin levels, kidney plays a role in elimination, did not reduce insulin sensitivity			BMI, body fat, HOMA-R, insulin
Kawamura *et al.* (2010) [65]	3192	CKD	Serum resistin is higher in CKD population.	hsCRP, TG, HOMA	GFR, HDL	BMI
Kaynar *et al.* (2014) [66]	150	Tx	Resistin is not elevated in Tx patients	PEW		
Kielstein *et al.* (2003) [67]	30	HD	Resistin levels depend mainly on GFR and its levels do not modulate insulin sensitivity	Homocysteine, age	GFR	Insulin, leptin, BMI, waistCX
Malyszko *et al.* (2006) [68]	96	Tx	Kidney function is a major determinant of elevating resistin and inflammation	hsCRP, IL-6, RBCc, WBC, VCAM	GFR	
Marouga *et al.* (2013) [69]	80	CKD	Resistin may be a part of the reverse epidemiology phenomenon of CKD patients	TNF, hsCRP	Alb, GFR, Htc, BMI, leptin, HOMA	HOMA, BMI, cholesterine, leptin
Oltean *et al.* (2013) [70]	63	DBD	High resistin level in DABD causes delayed graft function			
Spoto *et al.* (2013) [71]	231	HD	Resistin predicts death depending on ADPN level	hsCRP	ADPN	Leptin, HOMA

abd.circ., abdominal circumference; ACE, angiotensin-converting enzyme; ADMA, asymmetric dimethylarginine; ADPN, adiponectin; Alb, albumin; ARB, angiotensin receptor blocker; BF, body fat; BMD, bone mineral density; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CCI, chronic coronary insufficiency; CKD, chronic kidney disease; CRP, C-reactive protein; CVD, cardiovascular disease; DABD, donation after brain death; DGF, delayed graft function; DM, diabetes mellitus; ED, endothelial dysfunction; FMD, fibromuscular dysplasia; GFR, glomerular filtration rate; HD, hemodialysis; HDL, high density lipoprotein; Hgb, hemoglobin; HOMA, homeostasis model assessment; hsCRP, high-sensitivity C-reactive protein; ICAM, intracellular adhesion molecule; IGT, impaired glucose tolerance; IL, interleukin; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy; MetSy, metabolic syndrome; NODAT, new-onset diabetes after transplantation; PAPP-A, pregnancy-associated plasma protein A; PEW, protein energy wasting; PTH, parathyroid hormone; RBC, red blood cell; RRT, renal replacement therapy; RTR, renal transplant recipients; SNP, single nucleotide polymorphism; TSAT, transferrin saturation; TG, triglyceride; TNF, tumor necrosis factor; Tx, transplantation; vitD, vitamin D; VCAM, vascular cell adhesion molecule; waistCX, waist circumference; WBC, white blood cell.

adiponectin levels are observed in healthy individuals. It is a 30-kDa plasma protein synthetized within adipose tissue, and it circulates in the blood as low and high molecular weight isoforms [78]. It activates the downstream signaling pathways through the AdipoR1 receptor, found in kidney cells and skeletal muscle, as well as the AdipoR2 receptor, located in the liver. In the general population, it is considered to be an anti-inflammatory adipocytokine that improves insulin sensitivity and offers cardioprotective benefits [79].

One of the largest adipocytokines is visfatin (52 kDa), which is largely synthesized and secreted by granulocytes and has recently been found to be an insulin sensitizer [56, 80]. Interestingly, endothelial cells within the uremic milieu have also been found to secrete visfatin [81]. While the exact pathways and functions of visfatin are still under investigation, it most likely activates insulin-like receptors and the tyrosine kinase pathway and has insulin-like, pro-inflammatory and anti-apoptopic actions [56, 80].

Resistin is another adipocytokine with metabolic functions and is known to cause insulin resistance. It is a 12.5-kDa cysteine-rich protein that is synthesized in different isoforms by macrophages [82–85]. It acts as a pro-inflammatory factor that increases the production of inflammatory cytokines and elevates the expression of cell adhesion molecules. While its exact biologic functions are still being elucidated, higher resistin levels have been associated with chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease, and resistin may play a role in the pathophysiology of atherosclerosis and endothelial cell injury [86, 87].

There are other adipocytokines, such as apelin, chemerin and omentin, that will not be discussed in detail in this article. These hormones have been recently discovered, and they are primarily expressed in visceral adipose tissue. For example, apelin synthesis is upregulated by nutritional and inflammatory markers, and it is negatively correlated with endothelial dysfunction [88]. In KTRs, lower apelin levels were associated with underlying cardiovascular disease (CVD) [89]. Moreover, lower apelin levels were observed and were found to be associated with endothelial damage and inflammation [89]. In addition, chemerin affects adipocyte differentiation and insulin signaling, and, despite positive correlations with inflammatory parameters and dyslipidemia, elevated levels have been associated with a survival advantage in dialysis patients [90]. Lastly, omentin's gene locus has been linked to diabetes and it is negatively correlated with inflammatory and nutritional parameters and positively correlated with plasma adiponectin levels, suggesting a protective role [91, 92].

Less is known about adipocytokines' functions and associations with outcomes within KTRs. To better inform the field, we analyzed these associations using one of the largest prevalent KTR cohorts (MINIT-HU) with measured adipocytokines [93–98]. In this study, we collected sociodemographic information, clinical parameters, medical and transplant history and laboratory data from 993 prevalent KTRs who were followed within a single ambulatory transplant clinic at the Department of Transplantation and Surgery, Faculty of Medicine, Semmelweis University in Budapest, Hungary, during the period of 31 December 2006–31 December 2007 [93–98]. Table 2 shows the correlations of the measured adipocytokines in this population, which will be discussed later in this article.

Table 2. Correlations in 988 renal transplant recipients

	Leptin		Adiponectin		Resistin	
	Correlation coefficient	P-value	Correlation coefficient	P-value	Correlation coefficient	P-value
Demographic data						
Age	0.08	0.02	0.08	<0.01	−0.05	0.12
Charlson comorbidity index	0.03	0.43	0.13	<0.01	<0.01	0.89
ESRD time	−0.02	0.58	0.09	<0.01	0.1	<0.01
Kidney-related parameters						
eGFR	−0.22	<0.01	−0.25	<0.01	−0.45	<0.01
Inflammatory markers						
TNF-α	0.06	0.08	0.07	0.04	0.21	<0.01
CRP	0.09	<0.01	0.02	0.55	0.18	<0.01
IL-6	0.09	<0.01	0.08	0.01	0.11	<0.01
Nutritional parameters						
BMI	0.48	<0.01	−0.19	<0.01	−0.11	<0.01
Abdominal circumference	0.31	<0.01	−0.22	<0.01	−0.08	0.02
HDL cholesterol	−0.02	0.54	0.34	<0.01	−0.13	<0.01
LDL cholesterol	0.02	0.44	−0.01	0.70	−0.12	<0.01
Cholesterol	0.10	0.00	0.12	<0.01	−0.1	<0.01
Adipocytokines						
Leptin			−0.04	0.18	0.0472	0.1402
Resistin	0.05	0.14	0.13	<0.01		
Adiponectin	−0.04	0.18			0.13	<0.01
Transplantation-related data						
Cold ischemic time	0.06	0.07	0.07	0.03	0.07	0.04
PRA mean	0.04	0.24	0.05	0.14	0.06	0.06
HLA mismatch	−0.07	0.03	0.02	0.45	−0.04	0.17

ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; TNF, tumor necrosis factor; IL, interleukin; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PRA, panel reactive antibodies; HLA, human leukocyte antigen.

Levels of adipocytokines in the serum

Adipocytokine concentrations are typically measured in serum, although normal ranges have not yet been defined in KTRs. Inflammation may potentially induce production, and given that the kidneys play a primary role in many of these hormones' clearance, impaired renal function may lead to higher circulating adipocytokine levels.

Prior data have shown that the kidney function has a modulating effect on leptin levels. Cumin *et al.* [99] demonstrated that leptin clearance is eliminated following bilateral nephrectomy in rats. Additionally, studies also suggest that leptin is filtered through the glomerulus and degraded in the proximal tubule by megalin [73, 100, 101]. In addition, small proportions of leptin have been observed in urine in animals as well as humans [102–104]. These findings indicate that in KTRs, leptin levels may be elevated in the context of impaired renal function and possibly by the uremic milieu [105, 106]. In the non-obese population, levels typically range from 5 to 10 ng/mL, while in obese subjects levels may be 10-fold higher in healthy persons with normal kidney function [107, 108]. In patients with impaired kidney function, hyperleptinemia with levels up to 490 ng/mL have been observed [109]. Some studies suggest that uremia may be associated with higher leptin levels, while others suggest that only nutritional parameters modulate these hormones [110–112].

In contrast, leptin's counterpart, adiponectin, is downregulated in patients with obesity. In diabetic populations, plasma concentrations typically range between 5 and 30 μg/mL, with higher levels observed in those who are female and of older age [113, 114]. Adiponectin is metabolized by the liver, and metabolites are eliminated by the kidneys [115]. Adiponectin molecules may be filtered via the glomerulus, and they are detected in renal arteriole muscle and endothelial cells, as well as within proximal and distal tubules. Proximal tubule cells can synthesize and secrete adiponectin and can therefore be measured in urine [116, 117]. In patients with impaired kidney function, serum adiponectin levels are elevated. The uremic milieu and pro-inflammatory cytokines impair adiponectin synthesis as biofeedback for impaired renal elimination [118].

While the pathways by which visfatin is metabolized and eliminated are still under investigation, it is thought that the kidney plays an important role in its biodegradation. In a study of metabolic syndrome patients, the mean ± standard deviation of visfatin concentrations was 3.8 ± 8.8 ng/mL [119]. Visfatin levels are typically elevated in patients with CKD, including those undergoing hemodialysis, although a recent large cohort study suggested that levels only correlated with inflammation and insulin resistance and not with kidney function [50, 120]. Moreover, in a study of >3000 patients by Kocelak *et al.* [121], it was found that visfatin levels were not associated with kidney function, although the cohort was largely comprised of elderly patients. In a study of KTRs, higher visfatin concentrations were observed (37 ± 14 ng/mL), although higher levels were also observed in the healthy control group (28 ± 11 ng/mL) [56].

The normal range of resistin has not been defined, although in one study of healthy volunteers by Spoto *et al.* [122] it was found that levels ranged between 1.2 and 29.9 ng/mL. Some studies suggest that resistin functions as a pro-inflammatory cytokine and its serum level may be elevated by inflammatory parameters [123]. In CKD patients, strong correlations between resistin and kidney function have been observed [124]. Futhermore, Malyszko *et al.* [125] demonstrated that hemodialysis patients with residual kidney function had significantly lower resistin levels than those without residual kidney function, supporting the hypothesis that resistin is cleared via the kidney.

Based on these data (Table 1), there does not appear to be a strong, if any, correlation between leptin and glomerular filtration rate, although there does appear to be a correlation between leptin and nutritional parameters. In contrast, adiponectin levels are decreased in obese patients, but higher levels are observed with impaired kidney function. Kidney function, as well as inflammation, also appears to have a substantial impact on visfatin and resistin levels. Table 2 also indicates a correlation between adipocytokines and graft function.

Adipocytokines and nutritional status

Adipocytokines modulate appetite and nutritional status in KTR and CKD patients. Leptin is the primary hormone that regulates satiety and maintains body weight. In healthy subjects, an increase in body weight results in higher leptin levels and subsequent reduction in hunger [126]. Higher leptin levels may also lead to anorexia by binding to melanocortin-4 receptors (MC4-R), and inhibition of peripheral MC4-R can reduce muscle atrophy and improve anorexia via insulin-like growth factor-1 (IGF-1) [127]. As such, higher leptin concentrations due to impaired kidney function may contribute to protein energy wasting (PEW).

Adiponectin is considered to be an anti-inflammatory cytokine and also plays a key role in metabolic syndrome. In experimental studies, higher adiponectin levels have been shown to decrease high-density lipoprotein (HDL) levels, vis-à-vis apolipoprotein A1 and dysregulation of hepatocytes [128]. Elevated adiponectin levels may also lead to malnutrition via weight loss due to increased energy expenditure [129]. It has been observed that malnourished patients on renal replacement therapy have higher adiponectin levels [130].

Visfatin is a pro-inflammatory cytokine synthesized by macrophages embedded in visceral adipose tissue. In non-obese individuals, there is a similar degree of visfatin production in subcutaneous and visceral fat tissue, while in obese patients visceral synthesis is more prominent [131, 132]. At this time, the association between visfatin and nutritional status remains unclear [50, 132–136]. In a study by Carrero *et al.* [50], visfatin was not linked with nutritional parameters in Stage 5 CKD patients, although it was observed that higher serum visfatin levels were associated with increased satiety. Considering that CKD patients have higher visfatin levels, and that visfatin is associated with reduced appetite, it has been suggested that this hormone is part of the PEW syndrome.

Resistin was recently discovered as a hormone that causes insulin resistance in rodents, although these findings are still under investigation in humans. In obese rodents, higher resistin concentrations were observed, which positively correlated with dyslipidemia. It has also been suggested that a reduction of serum resistin levels with antibody neutralization might improve insulin sensitivity [137–139]. Obese individuals have higher resistin levels that persist even with weight gain or loss [140]. It has been suggested that resistin may link PEW to inflammation, since patients with a lower body mass index (BMI) have higher levels of inflammatory factors as well as resistin levels [66, 69].

Adipocytokines in inflammation and their effects on kidney cells

Figure 1 shows the potential mechanisms of adipocytokines on kidney cells. Leptin acts as a pro-inflammatory factor, stimulating the production of pro-inflammatory cytokines [141]. It activates neutrophil and monocyte cell phagocytosis and reactive

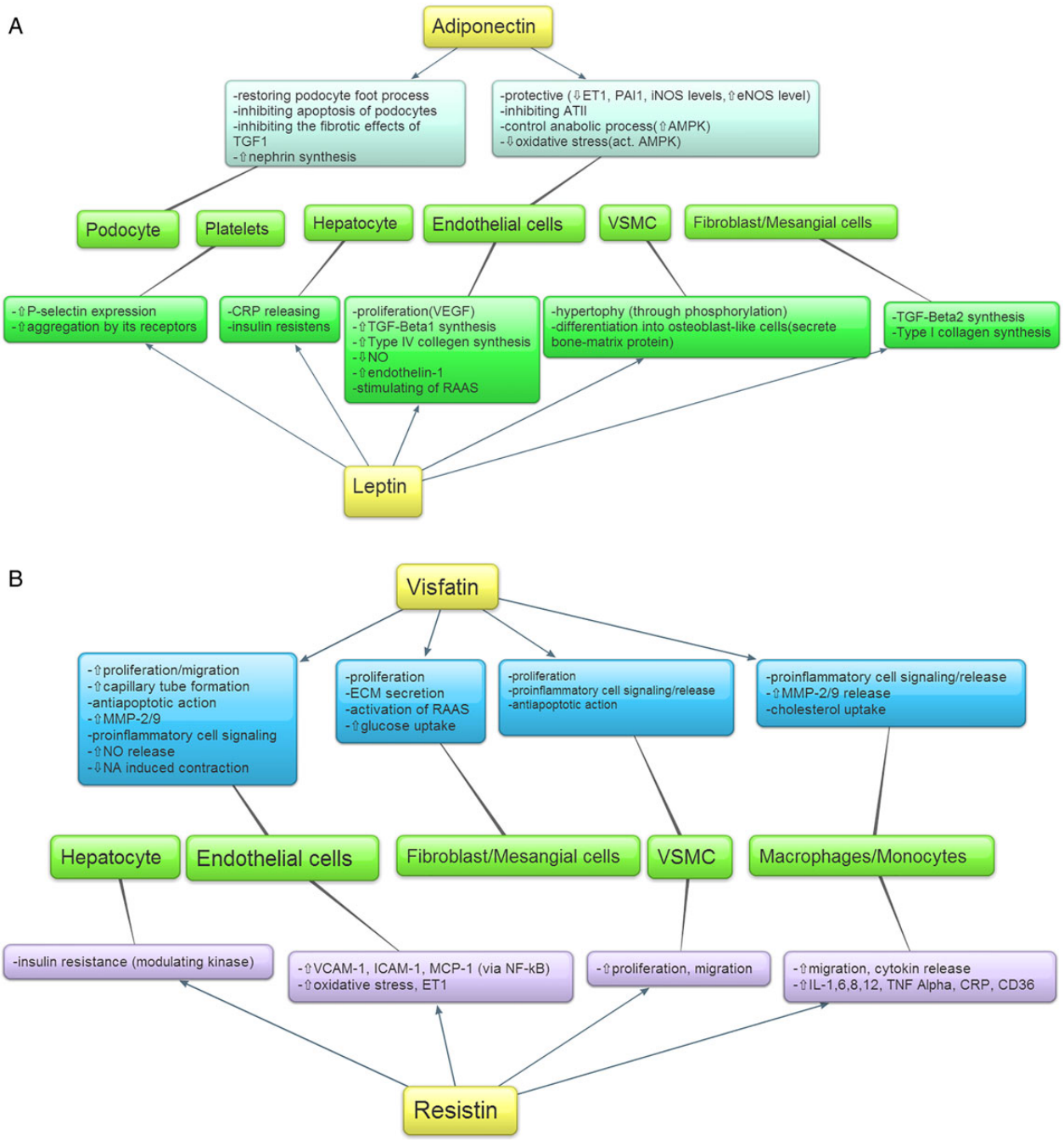

Fig. 1. (**A**) Effects of leptin and adiponectin on different types of cells. (**B**) Effects of visfatin and resistin on different types of cells. ATII, angiotensin II; CRP, C-reactive protein; ECM, extracellular matrix; eNOS, extracellular nitric oxide synthetase; ET1, endothelin-1; ICAM, intracellular adhesion molecule; IL, interleukin; iNOS, inducible nitric oxide synthetase; MCP, methyl-accepting chemotaxis protein; MMP, matrix metalloproteinase; Na, sodium; NF-kB, nuclear factor κB; NO, nitric oxide; PAI1, plasminogen activator inhibitor-1; RAAS, renin-angiotensin-aldosterone system; RAAS, renin–angiotensin–aldosterone system; TGF, transforming growth factor; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor; VSMC, vascular smooth muscle cell.

oxygen species through natural killer cells [142, 143]. Leptin also alters the adaptive immune system by activating $CD4^+$ T lymphocytes and signaling negatively for $CD25^+$ T regulatory cells [144]. It has been hypothesized that the inactivity of regulatory T cells might lead to graft loss since stimulated $CD4^+CD25^+$Foxp3 regulatory T cells prevent rejection, although this has not yet been confirmed in studies [145]. In addition, some *in vitro* studies suggest that stem cell incubation in a leptin-rich environment induces granulocyte formation [146].

The location of adipocytokine receptors bears particular relevance, given their central role in the activation of intracellular pathways. Leptin receptors are expressed in different areas of the kidney, including the inner medulla and vascular structures in the corticomedullary region [147–149]. Within endothelial cells, leptin increases sodium excretion and diuresis by decreasing sodium–potassium channel activity and reducing nitrogen monoxide (NO) production, inhibiting its protective role [150–154]. Within glomerular endothelial, mesangial and vascular smooth muscle

cells, leptin induces proliferation and size increases by activating the mitogen-activated protein kinase (MAPK) pathways [155–157]. Moreover, it induces hypertrophy through different factors causing thickening of the basement membrane. Lastly, leptin also activates the renin–angiotensin–aldosterone system (RAAS) [156, 158, 159]. Observational studies have not found an association between leptin and inflammation in KTRs (Tables 1 and 2).

In contrast to leptin, adiponectin functions as an anti-inflammatory cytokine. Adiponectin enhances anti-inflammatory cytokine synthesis, inhibits angiotensin II–induced inflammation and decreases albuminuria. Recent findings suggest that adiponectin activates nuclear factor κB (NF-κB) transcription. NF-κB is a protein kinase that regulates the immune system through T-cell activity and plays an important role in acute rejection [160]. Furthermore, some but not all data suggest that adiponectin has regulatory effects on T cells. The anti- and pro-inflammatory effects may change according to the molecular isoform of adiponectin [161, 162].

Receptors of adiponectin are also present in kidney cells. Through AdipoR1 it activates the adenosine monophosphate (AMP)–activated protein kinase (AMPK) pathway, inducing protective processes. Within podocytes, adiponectin restores foot processes and inhibits apoptosis, fibrotic effects of TGF-1, nephrin and Nox4 synthesis. Within endothelial cells, it downregulates pro-inflammatory and vasoconstrictor factors and oxidative stress. Furthermore, it elevates endothelial nitric oxide synthase (NOS) concentration and controls anabolic processes [163]. In summary, adiponectin may have protective effects on kidney, although higher levels have not been associated with better graft survival in KTRs [21]. Indeed, adiponectin has demonstrated weak associations with inflammatory parameters in KTRs (Tables 1 and 2).

Resitin's and visfatin's exact receptors are still unknown. Both facilitate the synthesis of inflammatory cytokines within mononuclear and endothelial cells and inhibit the apoptosis of macrophages. They also promote the expression of cell adhesion molecules and chemotaxis [85, 164–168]. Within endothelial cells, they activate NF-κB transcription factors that augment inducible NOS concentrations and increase the release of endothelin-1 and NO. Visfatin also promotes proliferation and capillary tube formation [81, 168–173]. Moreover, visfatin activates superoxide production, inducing glomerular permeability and RAAS [174–176]. Visfatin and resistin are important factors of inflammation in KTRs (Tables 1 and 2).

It should be noted that strong associations have been observed between visfatin and $CD68^+$ macrophages [135]. $CD68^+$ macrophage accumulation has been observed in acute rejection, although further investigation is needed to determine this relationship. Specifically for resistin, Akagun *et al.* [61] demonstrated that patients receiving hemodialysis with failed kidney allografts had significantly higher resistin levels than those without allografts, suggesting that resistin may play a role in chronic inflammation.

In conclusion, higher adipocytokines observed in the context of impaired kidney function may be due to not only reduced clearance, but also to kidney degradation through inflammatory pathways leading to death and graft loss in KTRs.

Adipocytokines role in transplant comorbidities

Pro-inflammatory adipocytokines may lead to hypertension, insulin resistance, CVD and chronic or acute inflammation [177]. In KTRs with impaired allograft function receiving immunosuppression therapy, adipocytokines may contribute to the development of posttransplant bone disease, anemia, cardiovascular morbidity, new-onset diabetes after transplantation (NODAT) and cancer.

Given that the kidney is one of the major end-organs regulating mineral homeostasis, impaired kidney function may lead to metabolic bone disease. Leptin may in fact accelerate bone metabolism by activating and converting vascular muscle cells into osteoblasts [178]. In epidemiological studies, parathyroid hormone and leptin have shown a negative correlation, and higher leptin levels have been associated with reduced bone turnover [11, 179]. Additionally, leptin causes oversynthesis of fibroblast growth factor 23, subsequently altering the regulation of phosphate homeostasis [180].

Impaired kidney function is the main cause of secondary anemia because of reduced erythropoietin production. Interestingly, leptin receptors may be found in hematopoietic stem cells and higher leptin production has been observed in bone marrow [181]. In epidemiological studies, serum leptin levels are a stronger predictor of erythropoietin sensitivity than body fat and are strongly associated with hemoglobin [182–184]. Erythropoietin stimulating agents (ESAs) administered to CKD patients with higher leptin levels seem to be less effective [182]. A correlation was also observed between serum leptin and erythropoietin resistance in KTRs [96].

Cardiovascular disease is the leading cause of morbidity and mortality among KTRs. Adiponectin presumably has a protective role in the pathogenesis of CVD. Adiponectin receptors are present in endothelial and vascular muscle cells and may reduce oxidative stress, atherosclerosis, fibrosis and proliferation. In the general population, observational studies suggest that lower adiponectin levels are associated with higher cardiovascular mortality [185, 186]. For example, in the LANDMARK 2 study, there was an inverse correlation between adiponectin, inflammation and nutrition in KTRs; furthermore, male patients with lower adiponectin levels had higher CVD risk [30, 187]. However, other data in KTRs have shown positive correlations between higher adiponectin levels and lower survival rates [21]. In a study by Sahin *et al.* [188], adiponectin levels were significantly higher in patients receiving cyclosporine compared with those on tacrolimus. Malgorzewicz *et al.* [189] suggested that higher leptin levels in obese patients are a risk factor for CVD and chronic rejection. They also demonstrated that patients with a BMI >25 kg/m^2 had significantly higher leptin:adiponectin ratios, and those obese patients with higher leptin:adiponectin ratios had a greater risk for cardiovascular events. According to Nicoletto *et al.* [16], 5 years after transplantation, patients' leptin, insulin resistance and lipid profiles were similar to the pretransplantation period. This metabolic profile is possibly associated with the higher incidence of CVD observed in the late posttransplantation period. Visfatin and resistin play an important role in the development of endothelial dysfunction that may lead to CVD. For example, higher visfatin levels have been observed in patients with coronary artery disease and atherosclerotic plaques [190–192]. Additionally, Weikert *et al.* [193] demonstrated that patients in the highest resistin quartile had a 2-fold higher risk of myocardial infarction than patients in the lowest quartile. In a prospective study of 2739 participants from the Framingham Offspring Study followed for 6 years, Frankel *et al.* [194] demonstrated that higher resistin levels were associated with a higher risk of incident heart failure.

Epidemiological data suggest that the prevalence of NODAT ranges from 4 to 25% in KTRs [195]. In one observational study, lower pretransplantation adiponectin levels were an independent predictor of NODAT [196]. Recently, Romanowski *et al.* [197] found a significant association between the leptin gene allele

and posttransplant diabetes, and it is thought that the 276G/T adiponectin gene polymorphism is also responsible for NODAT. Shu *et al.* [198] also examined various adipocytokines in KTRs with and without metabolic syndrome and found that metabolic syndrome was associated with significantly higher leptin, adiponectin, resistin and visfatin levels. Observational studies have not yet demonstrated an association between visfatin and glucose metabolism, but in animal studies visfatin has been found to have a protective effect on pancreatic beta cells [119, 199–201]. While resistin's role in diabetes is still under investigation, Shu *et al.* [198] have demonstrated strong associations between the presence of the metabolic syndrome and higher serum resistin levels.

Microalbuminuria is an important hallmark of worsening kidney function. Yano *et al.* [202] found that adiponectin is associated with low-grade albuminuria in obese and lean nondiabetic patients. Following multivariable adjustment, urine albumin excretion was significantly higher among patients with lower versus higher adiponectin levels. Several other studies suggest that lower adiponectin levels correlate with albuminuria in obese and diabetic patients [203]. In an observational study including patients with type 1 diabetes mellitus, Prior *et al.* [204] demonstrated strong positive associations between serum adiponectin and plasma antioxidant status. This correlation was most relevant in patients with albuminuria, suggesting an association between higher adiponectin levels, antioxidant status and reduced oxidative cellular burden.

It is well established that immunosuppression therapy heightens the risk of malignant disorders [205]. In some forms of cancer, adiponectin receptors have been found within malignant cells [206]. Recent data have also shown that lower adiponectin levels are associated with a higher incidence of colorectal and prostate cancer [207]. In spite of these findings, locally elevated adiponectin levels have been observed in chondrosarcoma, where adiponectin has been shown to increase the expression of vascular endothelial growth factor [206].

Adipocytokines and outcomes in KTRs

There are limited data regarding the association between adipocytokines and outcomes in patients with end-stage renal disease. Epidemiological studies suggest that leptin declines after kidney transplantation and that it correlates with nutritional parameters. In CKD patients, lower leptin concentrations predict mortality, although there has been only one study examining the association between leptin, mortality and graft loss in KTRs [208, 209]. Similar to other nutritional factors, higher leptin levels are associated with higher mortality risk in patients undergoing hemodialysis [210]. Another notable finding is that leptin deficiency has been associated with prolonged graft survival, suggesting that lean individuals with lower leptin levels may benefit from kidney transplantation [209]. This hypothesis is supported by data from Fonseca *et al.* [6], who found that decreases in leptin levels pre- and posttransplantation were associated with less delayed graft function since higher levels may increase the risk of graft loss; however, these relations require more investigation.

There have been comparatively more observational data assessing the role of adiponectin in KTRs. Only a few articles have examined the association between adiponectin and mortality. Similar to studies of adiponectin and mortality in hemodialysis patients [211], we found that higher levels of adiponectin were associated with increased mortality, but not graft loss, despite the protective effects of adiponectin [21]. Roos *et al.* [39] found that low pretransplant adiponectin levels predicted risk of graft loss, which may be due to atherogenic pathways. It should also be highlighted that, according to Fonseca *et al.* [6], early graft function is not a primary modifier of adiponectin levels since there were no significant differences in serum adiponectin levels among those with preserved versus impaired graft function.

A number of studies have examined visfatin in patients with impaired renal function (Table 1). However, only two articles have investigated its association with outcomes in KTRs, suggesting that levels decline after transplantation and correlate with the parameters of endothelial dysfunction [56, 59]. Axelsson *et al.* [48] demonstrated that higher visfatin levels were associated with higher mortality in CKD.

Numerous studies have examined the role of resistin in mortality among patients with impaired kidney function, although few in the KTR population (Table 1). Spoto *et al.* [122] analyzed the association between resistin and all-cause and cardiovascular mortality among KTRs and found significant associations between serum resistin and death, although serum adiponectin appeared to be a potent effect modifier of this relationship. In contrast, Chung *et al.* [212] found that lower serum resistin concentrations were associated with lower survival rates in patients on hemodialysis. Our results also suggest that higher resistin levels have a dose-dependent relationship with risk of graft loss and mortality even after multivariable adjustment in KTRs [213]. We found that for every 10 ng/mL elevation of serum resistin level there is a 30% increased mortality risk and 73% increased risk of graft loss [213].

One of the major limitations of these collective studies is that they have typically examined adipocytokine concentrations at a single point in time; therefore, they cannot examine changes in levels over time. In addition, most were of small sample size and were unable to examine cause-specific mortality. At this time, further studies of adipocytokines are needed in the field of transplantation.

Conclusion

Adipocytokine levels are often elevated in patients with kidney disease, including KTRs with impaired graft function. These cytokines have been associated with endothelial dysfunction, inflammation and malnutrition, which may contribute to the degradation of kidney tissue. Higher leptin levels might play a role in rejection through the regulation of macrophages. Adiponectin also has important regulatory effects on the adaptive immune system and may have a role in rejection. In addition, few studies have shown that these adipocytokines are independent predictors of survival in KTRs. Further studies are needed to understand the role of adipocytokines in the nutritional status, graft function and survival of KTRs.

Conflict of interest statement

None declared.

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