ORIGINAL ARTICLE

Obesity and chronic kidney disease progression—the role of a new adipocytokine: C1q/tumour necrosis factor-related protein-1

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ABSTRACT

Background. Obesity is a risk factor for incident chronic kidney disease (CKD) in the general population. C1q/tumour necrosis factor-related protein 1 (CTRP1) is a new adipokine with multiple vascular and metabolic effects and may modulate the association between obesity and vascular diseases. The aim of the study is to explore potential links between obesity, CTRP1 levels and CKD progression.

Methods. Patients with Stages 3 and 4 CKD without previous cardiovascular events were enrolled and divided into two groups according to body mass index (BMI). Demographic, clinical and analytical data and CTRP1 levels were collected at baseline. During follow-up, renal events [defined as dialysis initiation, serum creatinine doubling or a 50% decrease in estimated glomerular filtration rate (Modification of Diet in Renal Disease)] were registered.

Results. A total of 71 patients with CKD were divided into two groups: 25 obese (BMI >30 kg/m^2) and 46 non-obese. CTRP1 in plasma at baseline was higher in obese patients [median (interquartile range) 360 (148) versus 288 (188) ng/mL, P = 0.041]. No significant association was found between CTRP1 levels and CKD stage, presence of diabetes, aldosterone and renin levels, or blood pressure. Obese patients had higher systolic blood pressure (P = 0.018) and higher high-sensitivity C-reactive protein (P = 0.019) and uric acid (P = 0.003) levels, without significant differences in the percentage of diabetic patients or albuminuria. During a mean follow-up of 65 months, 14 patients had a renal event. Patients with CTRP1 in the lowest tertile had more renal events, both in the overall sample (log rank: 5.810, P = 0.016) and among obese patients (log rank: 5.405, P = 0.020). Higher CTRP1 levels were associated with slower renal progression (hazard ratio 0.992, 95% confidence interval 0.986–0.998; P = 0.001) in a model adjusted for obesity, aspirin, albuminuria and renal function.

Conclusions. CTRP1 levels are higher in obese than in non-obese patients with CKD. High CTRP1 levels may have a renal protective role since they were associated with slower kidney disease progression. Interventional studies are needed to explore this hypothesis.

Keywords: adipokine, chronic kidney disease, CTRP1, obesity, progression

INTRODUCTION

Obesity, the 21st century epidemic, is a systemic disease that carries a markedly increased risk for comorbidities such as type 2 diabetes mellitus (DM), hypertension, dyslipidaemia, cardiovascular disease and chronic kidney disease (CKD) [1–5]. In addition, obesity has been linked with CKD progression to end-stage renal disease [6, 7] although the mechanism of this last association is not completely understood. Although the indirect effects of obesity on the kidney are well known, mainly through the development of other risk factors for CKD such as DM and hypertension [7], the molecular mechanisms of the direct impact of obesity are still to be elucidated.

Adipose tissue is no longer believed to be a passive 'energy storage' tissue but a 'living organ' that secretes adipokines, proteins synthesized by adipocytes with many paracrine and endocrine functions. Complement C1q/tumour necrosis factor-related proteins (CTRPs) are a family of recently discovered adiponectin paralogues [8]. Within this family, CTRP1 has attracted the most interest. CTRP1 is a secreted glycoprotein adipokine composed of 281 amino acids. It is primarily expressed and secreted by the stromal-vascular cells and visceral adipose tissue and marginally by the zona glomerulosa of the adrenal cortex and vascular wall tissue [9]. Plasma CTRP1 levels exhibited in humans significant association with body mass index (BMI) [10], type 2 DM [11] and congestive heart failure [12] and is thought to play a role in several metabolic pathways. As CTRP1 enhances glucose uptake and insulin sensitivity [13], it has been proposed as a negative feedback regulator in DM. It may also be a link between obesity and hypertension since it enhances aldosterone secretion [9, 14].

Up to now, there are no reports of circulating CTRP1 levels in CKD patients, and no relationship has been described between this adipokine and renal disease progression. The aims of this study are to measure CTRP1 levels in CKD patients and to evaluate the relationship between obesity, CTRP1 and CKD progression.

MATERIALS AND METHODS

This is a prospective study enrolling patients without previous cardiovascular disease (CVD) who had Stage 3 or 4 CKD [estimated glomerular filtration rate (eGFR) between 60 and 15 mL/min/1.73 m^2 of body surface area], according to the four-variable Modification of Diet in Renal Disease (MDRD4) equation, who participated in the the Effect of Aspirin in Primary Prevention of Cardiovascular Risk in Patients With Chronic Kidney Disease (AASER) study [clinical trial (ClinicalTrials.gov Identifier: NCT01709994)].

A total of 71 patients were included in the study: 18 Stage 3a (eGFR 45–59 mL/min/1.73 m^2), 34 Stage 3b (eGFR 30–44 mL/min/1.73 m^2) and 19 Stage 4 (15–29 mL/min/1.73 m^2). A total of 22 patients were diabetic: 7 were obese and 15 non-obese. Inclusion and exclusion criteria are detailed in Supplementary data, Appendix A.

Visits were performed every 6 months, and the following data were collected in all participants (at every visit):

- anthropometric/clinical data: age, gender, height, weight, BMI, systolic and diastolic blood pressure, and heart rate;

- medical history including data on DM and cardiovascular risk factors such as dyslipidaemia and hypertension;
- concomitant medication: renin–angiotensin system blockers, statins and allopurinol. The dosage of antihypertensive drugs, lipid-lowering and uric acid lowering agents was adjusted following the Kidney Disease: Improving Global Outcomes guidelines. Changes in the dosage or choice of drug were not recorded during the follow-up; and
- laboratory data: serum creatinine, haemoglobin, lipid parameters, sodium, potassium, serum fibrinogen, erythrocyte sedimentation rate, white cell count and high-sensitivity C-reactive protein (hsCRP) were assessed using standard laboratory methods. In first-morning urine sample, albumin/creatinine ratio (ACR) was measured, and in 24-h urine samples, albuminuria, sodium and potassium.

The following laboratory data were only measured at baseline:

- CTRP1, aldosterone, renin, aldosterone/renin ratio.

The MDRD4 equation was used to estimate GFR. Plasma hsCRP was measured using a latex-based turbidimetric immunoassay on a Hitachi analyser (Sigma Chemical Co). Aldosterone, renin concentration and plasma renin activity were measured using commercially available chemiluminescent (CLIA) kits {LIAISON® Aldosterone (REF 310450), Diasorin Inc, MN, USA and LIAISON® Direct Renin [(REF) 310470], Diasorin SpA, Italy} following the manufacturer's instructions. Plasma CTRP1 was measured at baseline. CTRP1 concentrations were measured using a commercially available ELISA kit (BioVendor, Inc., Czech Republic; catalogue number: RD191153100R) according to the manufacturer's protocol.

Participants were followed for a mean (±SD) of 64.8 ± 16.4 months. The study was approved by the local Ethics Committees in accordance with the Declaration of Helsinki and all patients provided written informed consent.

Renal event was defined as doubling of serum creatinine, an eGFR decrease ≥50% or initiation of renal replacement therapy. The researchers adjudicated renal events according to clinical documentation.

Statistical analysis

All statistical analyses were performed using IBM SPSS, version 21.0 (IBM Corp., Armonk, NY, USA) for Windows. Values are expressed as median (interquartile range). Participants were categorized by baseline BMI as non-obese (<30 kg/m^2) and obese patients (>30 kg/m^2). Differences between obese and non-obese patients were analysed by Mann–Whitney test. Kaplan–Meier curves and the log-rank test were used to analyse renal survival. For an exploratory survival analysis, the patients were divided into two groups based on the tertiles of CTRP1 levels: the lowest tertile was compared with the other tertiles. Cox proportional hazard models were used to evaluate the risk of renal events, and the results were adjusted for several covariates. Statistical significance is defined as a two-tailed P < 0.05.

Table 1. Baseline characteristics of the study cohort

Variables	Non-obese (n = 46)	Obese (n = 25)	P-value
Age (years)	66 (16)	68 (9.5)	0.310
BMI (kg/m^2)	**26.6 (3.1)**	**32 (3.5)**	**<0.001**
Diabetes, n (%)	15 (32.6)	7 (28)	0.68
SBP (mmHg)	**136 (17)**	**143 (18)**	**0.018**
DBP (mmHg)	76 (12)	80 (50)	0.138
Haemoglobin (g/dL)	14.0 (2.3)	13.3 (2.2)	0.459
Leucocytes ($\times 10^3$)	7.5 (3.0)	7.8 (3.1)	0.276
Glycosilated haemoglobin (%)	6.0 (0.85)	6 (1.1)	0.864
Glucose (mg/dL)	102 (30)	96 (43)	0.617
Creatinine (mg/dL)	1.69 (0.68)	1.6 (0.83)	0.861
eGFR (mL/min/1.73 m^2)	38 (18)	35 (19)	0.509
CKD Stage 3, n (%)	35 (76)	17 (68)	0.462
Urea (mg/dL)	67(31)	71 (44)	0.354
Uric acid (mg/dL)	**6.5 (1.7)**	**7.5 (1.2)**	**0.003**
ACR (mg/g)	54 (217)	58 (139)	0.990
LDL-cholesterol (mg/dL)	117 (85)	105 (41)	0.427
HDL-cholesterol (mg/dL)	53 (22)	54 (17)	0.569
Triglycerides (mg/dL)	131 (73)	120 (68)	0.895

Data are expressed as median and interquartile range (IQR). Bold means statistically significant differences; p < 0.05.

SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Ethical approval

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments.

RESULTS

A total of 71 patients who participated in the AASER study [15] were included in the analysis of the association of obesity with renal disease progression. Participants were categorized by baseline BMI as non-obese (<30 kg/m^2) (n = 46) and obese patients (≥30 kg/m^2) (n = 25). Obese patients had higher systolic blood pressure (P = 0.018), serum uric acid (P = 0.003) and hsCRP (P = 0.019) as well as higher CTRP1 levels [360 (148) versus 288 (188) ng/mL; P = 0.041] than non-obese patients (Tables 1 and 2).

No differences were found in serum aldosterone, plasma renin, ACR, and urine sodium and potassium between obese and non-obese patients. CKD stages distribution was similar in both groups (Table 1). There were no significant differences between obese and non-obese in DM prevalence (32.6% versus 28%; P = 0.68) or in glycosylated haemoglobin in diabetic patients (7.2 ± 0.7% versus 7.8 ± 2.0%; P = 0.22). CTPR1 levels were similar between diabetic and non-diabetic patients [397.86 (282.70) versus 363.89 (139.73); P = 0.49].

There were no significant associations between CTRP1 plasma levels and baseline eGFR, uric acid or inflammation either in obese or non-obese patients. There was a slight negative correlation between CTRP1 and albuminuria in the non-obese group (P = 0.02), and a positive correlation between CTRP1 and aldosterone in the obese group (P < 0.01) (Table 3).

Use of renin–angiotensin system inhibitors was 93 and 88% in non-obese and obese patients (P = 0.42), respectively, use of statins 74 and 60% (P = 0.22), use of aspirin 32.6 and 52% (P = 0.11) and use of allopurinol 39 and 54% (P = 0.12).

Table 2. Baseline characteristics of the study cohort

Variables	Non-obese (n = 46)	Obese (n = 25)	P-value
Serum fibrinogen (mg/dL)	412 (133)	440 (110)	0.605
ESR (mm)	7 (14.5)	15 (16)	0.054
hsCRP (mg/L)	**2.0 (5.1)**	**3.5 (8.5)**	**0.019**
Sodium (mEq/L)	140 (3.2)	141 (3.5)	0.357
Potassium (mEq/L)	4.6 (0.7)	4.7 (0.5)	0.690
Urine sodium (mEq/24 h)	120 (86)	152 (71)	0.382
Urine potassium (mEq/24 h)	52 (18)	59 (23)	0.457
Plasma aldosterone (ng/dL)	17.3 (14.7)	15.8 (15.7)	0.444
Renin activity (ng/mL/h)	7.6 (12.6)	7.1 (17.4)	0.995
Renin concentration (μUI/mL)	99 (215)	105 (208)	0.922
ARR	0.18 (0.52)	0.19 (0.32)	0.844

Data are expressed as median (IQR). Bold means statistically significant differences; $p < 0.05$.

ESR, erythrocyte sedimentation rate; hsCRP, high sensitivity C reactive protein; ARR, aldosterone/renin concentration ratio.

Table 3. CTRP1 correlations (Spearman's ρ)

Variables	Non-obese ρ	Non-obese P-value	Obese ρ	Obese P-value
eGFR (mL/min/1.73 m^2)	0.141	0.36	−0.025	0.91
SBP (mmHg)	0.134	0.37	−0.026	0.90
Uric acid (mg/dL)	−0.051	0.73	−0.221	0.28
hsCRP (mg/dL)	0.138	0.38	−0.111	0.66
ACR (mg/g)	**−0.336**	**0.02**	0.203	0.32
Aldosterone (ng/dL)	0.026	0.68	**0.523**	**<0.01**
Renin activity (ng/mL/h)	0.102	0.51	0.329	0.11

eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

Renal outcomes

Fourteen patients reached the renal outcome (renal replacement therapy: eight patients; doubling of serum creatinine or ≥50% decrease in eGFR: six patients) after 64.8 ± 16.4 months of follow-up. Patients were divided according to CTRP1 tertiles. Seven renal events occurred at the lowest CTRP1 tertile and seven in the other tertiles in the global sample (log rank: 5.810, P = 0.016; Figure 1A). In the obese patients, two renal events occurred in the lower CTRP1 tertile and four events in the other tertiles (log rank: 5.405, P = 0.020; Figure 1B). Uric acid, systolic blood pressure and age did not increase the risk or renal events. Multiple Cox regression analysis showed that the higher CTRP1 levels [hazard ratio (HR) 0.992, 95% confidence interval (CI) 0.986–0.998; P = 0.012) the slower the renal disease progresses in a model adjusted for obesity (HR 3.125, 95% CI 0.790–12.355; P = 0.104), aspirin treatment (HR 0.907, 95% CI 0.208–3.956; P = 0.897), albuminuria (HR 1.001, 95% CI 1.000–1.002; P = 0.011) and baseline renal function (HR 0.910, 95% CI 0.845–0.979; P = 0.012) (Table 4).

DISCUSSION

Obesity is a well-established independent risk factor for incident CKD and decline in eGFR in the general population. In individuals with prevalent CKD, obesity is associated with a decline in eGFR in some but not in other studies [15–18]. CTRP1 may function as a novel adipokine that plays a crucial role in regulating obesity-linked vascular disease [11]. However, to date, there
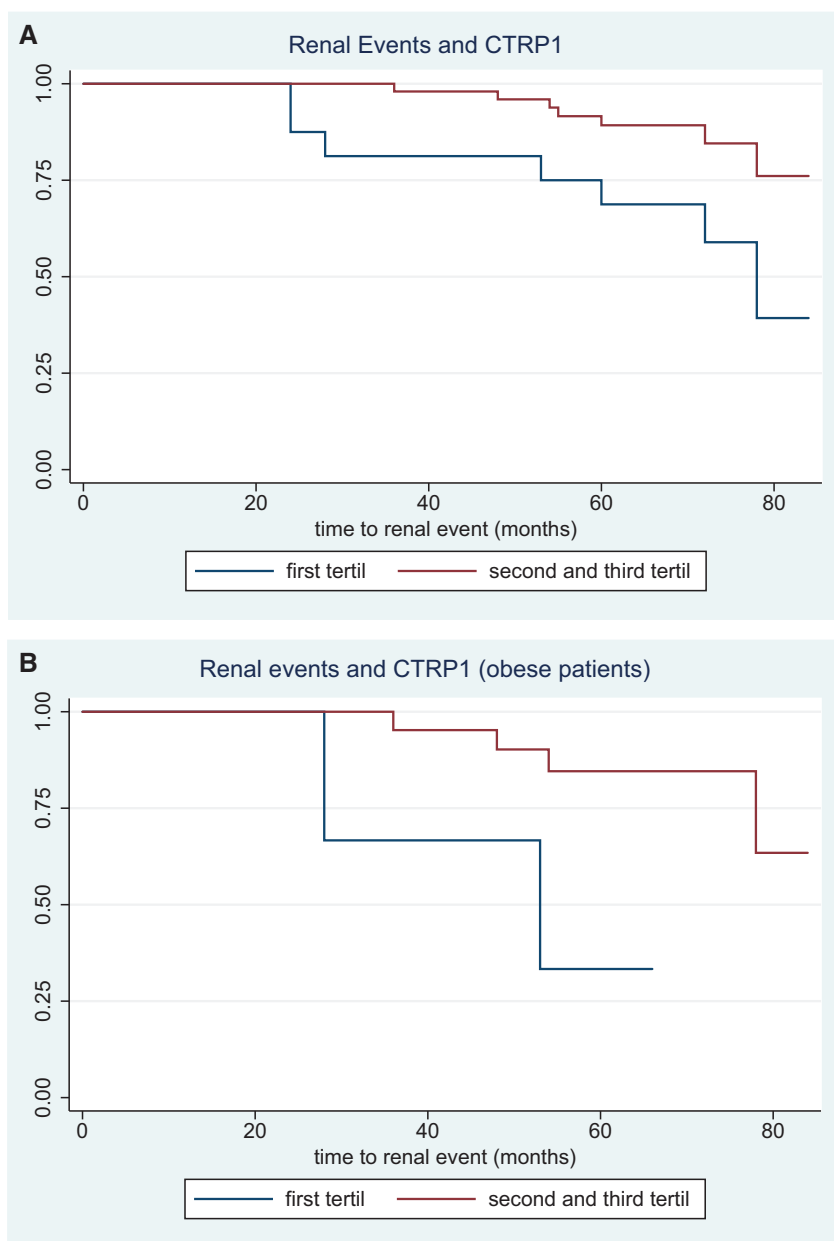
FIGURE 1: Renal outcomes according to CTRP1 tertiles in the global sample (**A**) and in obese patients (**B**). More renal events occurred at the lowest CTRP1 tertile in the global sample [log rank: 5.810, P = 0.016 (A)] and in obese patients [log rank: 5.405, P = 0.020 (B)].

Table 4. Cox regression analysis for renal events

Variables	Univariate model HR (95% CI)	P-value	Adjusted model 1 HR (95% CI)	P-value	Adjusted model 2 HR (95% CI)	P-value
CTRP1 (ng/mL)	0.996 (0.991–1.001)	0.091	0.992 (0.986–0.998)	0.010	0.992 (0.986–0.998)	0.012
Obesity	1.761 (0.605–5.123)	0.299	3.096 (0.786–12.198)	0.106	3.125 (0.790–12.355)	0.104
eGFR (mL/min/1.73 m^2)	0.916 (0.865–0.971)	0.003	0.909 (0.846–0.975)	0.008	0.910 (0.845–0.979)	0.012
ACR (mg/g)	1.000 (1.000–1.001)	0.064	1.001 (1.000–1.002)	0.005	1.001 (1.000–1.002)	0.011
Aspirin treatment	0.445 (0.124–1.601)	0.185			0.907 (0.208–3.956)	0.897
Uric acid (mg/dL)	1.375 (0.939–2.014)	0.102				
SBP (mmHg)	0.996 (0.991–1.001)	0.812				
Age (years)	0.990 (0.941–1.044)	0.830				

Model 1 included variables: CTRP1, obesity, eGFR and ACR; Model 2 included variables: CTRP1, obesity, eGFR, ACR and aspirin treatment.
SBP, systolic blood pressure.

are no data about CTRP1 levels in CKD patients and their possible association with or role in renal disease progression. For the first time, we showed that this new adipokine is increased in obese CKD patients and is associated with protection from CKD progression.

It is well established that adipose tissue produces a variety of secretory proteins, also known as adipokines, and that dysregulated adipokine production in obese individuals contributes to the pathogenesis of metabolic and cardiovascular diseases [19]. A highly conserved family of proteins homologous to adiponectin, sharing a C1q-like globular domain and a 3D organization resembling tumour necrosis factor (TNF)-α, were named the CTRP family for CTRPs [20]. CTRPs are paralogues of adiponectin and have emerged as important modulators of metabolic and inflammatory pathways. Based on rodent and clinical studies, CTRP1 has been suggested to have different functions in several tissues: muscle, liver, heart, adrenal cortex and vessels [21].

In the clinical context, CTRP1 has been correlated with BMI and reported to be increased in obese patients and in patients with atherosclerosis, coronary artery disease or metabolic disorders like insulin resistance and non-alcoholic fatty liver disease [8, 21].

CTRP1 has been suggested to exert beneficial actions on metabolic dysfunction, ischaemic heart disease and platelet function [21, 22]. Experimentally, transgenic overexpression of CTRP1 improves insulin sensitivity in obese mice [23]. CTRP1 also prevents collagen-induced platelet aggregation [24]. Recently, it has been shown that CTRP1-knockout mice have increased myocardial infarct size following ischaemia–reperfusion compared with wild-type mice. Conversely, systemic administration of CTRP1 attenuates myocardial damage in response to ischaemia–reperfusion in wild-type mice [25]. CTRP1 prevents neointimal formation, following mechanical arterial injury by suppressing vascular smooth muscle cell growth through the cAMP-dependent pathway [26]. On the other hand, CTRP1 has been proved to have proatherogenic and proinflammatory effects. It has been linked with enhanced secretion of proatherogenic factors like TNF-α, interleukin (IL)-1β and IL-6 [27] and with a concentration-dependent expression of adhesion molecules and inflammatory markers in human endothelial cells [28], all of them reverted in the presence of CTRP1 blockers.

Thus, CTRP1 plays a crucial but contradictory role in regulating obesity-linked vascular diseases, and it is still to be established whether CTRP1 is beneficial or detrimental for obese patients. Our study yields new information in this field. We found an association of CTRP1 levels with CKD progression in patients with CKD and obesity, suggesting a renoprotective role of CTRP1. To our knowledge, there are no experimental studies defining the role of the CTRP family in the kidney. In light of our results, this field deserves further investigations.

CTRP1 is expressed at high levels in adipose tissues of obese Zucker diabetic rats, specifically in the zona glomerulosa of the adrenal cortex, where aldosterone is produced. Indeed, CTRP1 dose-dependently promoted aldosterone production and expression of the aldosterone synthase CYP11B2 [9]. We found a positive correlation between aldosterone levels and CTRP1 only in the obese group although there were no differences in the mean aldosterone levels or renin activity in both groups. A possible explanation for these discrepancies could be that >90% of subjects in the study received treatment with renin–angiotensin system blockers and that these patients had moderate–advanced CKD that could modify this association.

In the diabetic state, in which adiponectin levels are low, CTRP1 was reported to be upregulated [11]. However, in our study, diabetic patients did not have higher CTRP1 levels, and there was no association between glycosylated haemoglobin and CTRP1 levels. Recently, it was reported that CTRP1 is overexpressed and shows a negative relationship with insulin resistance in type 2 diabetes [13]. Unfortunately, insulin resistance was not assessed in our study. CKD patients have greater insulin resistance than the general population. In addition, the number and type of anti-diabetic drugs used during the study have not been recorded. All these factors may explain the absence of relationship between diabetes and CTRP1.

Obesity is a well-established independent risk factor for incident CKD and decline in eGFR in the general population [2–5]. However, this relationship may reflect an indirect effect of obesity on the kidneys through the development of risk factors for incident CKD and renal disease progression such as hypertension, DM and dyslipidaemia. Several epidemiological studies [2, 3, 5, 29] show a U-shaped relationship between obesity and CKD progression, especially with BMIs <20 or >35 kg/m^2. However, this relationship disappears when models are adjusted for diabetes, hypertension and CVD. Despite this, there may be a direct effect of obesity in the kidneys. Obesity is an independent risk factor for the development of microalbuminuria in normotensive and non-diabetic patients [5, 30], especially in patients with higher visceral adiposity, and weight loss in morbidly obese patients attenuates proteinuria [31]. A specific pathological pattern has been described in the presence of obesity (obesity-related glomerulopathy), which is characterized by glomerulomegaly, focal or segmental glomerulosclerosis, decreased podocyte density and widened foot processes [32, 33]. Despite this, a specific genetic predisposition and/or a favourable renal environment may predispose to obesity-related nephropathy since most obese individuals never develop CKD [30] and up to 25% of 'metabolically healthy' obese individuals (without hypertension, DM or dyslipidaemia) may develop incident CKD [34, 35]. Between the various underlying mechanisms that link obesity and renal and cardiovascular damage, the most studied is the adipokine protein family. Adipokines like adiponectin, leptin and resistin may modulate kidney injury and function. Adiponectin improves insulin sensitivity and has an anti-inflammatory and antiproteinuric effect [36] and is decreased in obesity; whereas, leptin and resistin are increased in obese patients and cause hyperfiltration, proteinuria and renal oxidative stress [37–39]. CTRP1 may be predicted to share some of adiponectin's actions, but unlike adiponectin, it is increased in obese patients, and therefore, it could be one factor involved in the observed development of glomerulopathy and CKD progression in only some, but not all, obese individuals. Experimental studies have demonstrated that adiponectin deficiency in mice is associated with podocyte effacement and fusion, similar to findings in some patients with obesity and morbid obesity. These changes are accompanied by albuminuria and were not observed in mice without adiponectin deficiency. Adiponectin administration to mice reduced podocyte damage and led to the partial resolution of albuminuria [40]. However, the potential actions of CTRP1 on podocyte biology have not yet been characterized.

Clinical data on the role of obesity in CKD progression are scarce and contradictory. One study conducted in 125 patients with previous CKD showed that obesity could play a role in renal disease progression [15] and recently, it was reported that in 441 non-diabetic patients with autosomal-dominant polycystic kidney disease, obesity was strongly and independently

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associated with the rate of progression in early-stage CKD [18]. However, other studies in diabetic and non-diabetic patients did not confirm these findings [15, 17]. In our study, obesity did not increase the risk of renal events adjusted for baseline renal function and proteinuria although the sample size was too small to draw definite conclusions. We hypothesize that, similar to adiponectin, CTRP1 may protect the kidney of the obese patients by preventing podocyte damage. Although we did not find a relationship between albuminuria and CTRP1 levels, this may have been influenced by the widespread use of renin–angiotensin system blockers.

Several limitations of the study should be considered. The main limitation is the relatively small number of patients. In this regard, the low number of renal events precluded any definitive conclusions on the relationship between CTRP1, obesity and renal disease progression. Another limitation of the study is the absence of a healthy control group that allows to compare CTRP1 levels in CKD patients with individuals with normal renal function. However, the study also has strengths: it has a long follow-up time and the data are novel. In this regard, this is the first time that CTRP1 levels are explored in CKD patients, both obese and non-obese.

In summary, CTRP1 levels are increased in obese CKD patients and are associated with milder CKD progression, raising the hypothesis that, similar to adiponectin, CTRP1 might have a beneficial role in renal disease progression. This hypothesis should be tested by interventional experimental studies.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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AUTHORS' CONTRIBUTIONS

D.B. and M.G. analysed and picked the data. M.D.S.-N. measured CTRP1. All authors read and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

None declared.

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