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Macrophage inhibitory cytokine-1 (MIC-1/GDF15) and mortality in end-stage renal disease

Samuel N. Breit[1], Juan J. Carrero[2], Vicky Wang-Wei Tsai[1], Nasreen Yagoutifam[1], Wei Luo[1], Tamara Kuffner[1], Asne R. Bauskin[1], Liyun Wu[1], Lele Jiang[1], Peter Barany[2], Olof Heimburger[2], Mary-Ann Murikami[3], Fred S. Apple[3], Christopher P. Marquis[4], Laurence Macia[5], Shu Lin[5], Amanda Sainsbury[5], Herbert Herzog[5], Matthew Law[6], Peter Stenvinkel[2,*] and David A. Brown[1,*]

[1]St Vincent's Centre for Applied Medical Research, St Vincent's Hospital, University of New South Wales, Sydney, Australia, [2]Division of Renal Medicine, Karolinska University Hospital, Stockholm, Sweden, [3]Laboratory Medicine and Pathology, Hennepin County Medical Center, University of Minnesota School of Medicine, Minneapolis, MN, USA, [4]School of Biotechnology and Biomolecular Sciences, University of New South Wales, Sydney, Australia, [5]Neuroscience Program, The Garvan Institute for Medical Research, Sydney, Australia and [6]The Kirby Institute for infection and immunity in society, University of New South Wales, Sydney, Australia

Correspondence and offprint requests to: David A. Brown; E-mail: D.Brown@amr.org.au
* Both authors contributed equally to this work.

Abstract

Background. Elevated macrophage inhibitory cytokine-1 (MIC-1/GDF15) levels in serum mediate anorexia and weight loss in some cancer patients and similarly elevated levels occur in chronic kidney disease (CKD). Serum MIC-1/GDF15 is also elevated in chronic inflammatory diseases and predicts atherosclerotic events independently of traditional risk factors. The relationship between chronic inflammation, decreasing body mass index (BMI) and increased mortality in CKD is not well understood and is being actively investigated. MIC-1/GDF15 may link these features of CKD.

Methods. Cohorts of incident dialysis patients from Sweden ($n = 98$) and prevalent hemodialysis patients from the USA ($n = 381$) had serum MIC-1/GDF15, C-reactive protein (CRP) levels and BMI measured at study entry. Additional surrogate markers of nutritional adequacy, body composition and inflammation were assessed in Swedish patients. Patients were followed for all-cause mortality.

Results. In the Swedish cohort, serum MIC-1/GDF15 was associated with decreasing BMI, measures of nutrition and markers of oxidative stress and inflammation. Additionally, high serum MIC-1/GDF15 levels identified patients with evidence of protein-energy wasting who died in the first 3 years of dialysis. The ability of serum MIC-1/GDF15 to predict mortality in the first 3 years of dialysis was confirmed in the USA cohort. In both cohorts, serum MIC-1/GDF15 level was an independent marker of mortality when adjusted for age, CRP, BMI, history of diabetes mellitus and/or cardiovascular disease and glomerular filtration rate or length of time on dialysis at study entry.

Conclusions. MIC-1/GDF15 is a novel independent serum marker of mortality in CKD capable of significantly improving the mortality prediction of other established markers. MIC-1/GDF15 may mediate protein-energy wasting in CKD and represent a novel therapeutic target for this fatal complication.

Keywords: all-cause mortality; end-stage renal failure; hemodialysis; MIC-1/GDF15

Introduction

More than 15.5 million adults in the USA have moderately severe impairment of renal function. Of these, >480 000 are receiving active treatment for end-stage renal disease and >100 000 new patients start treatment annually [1]. Of the patients receiving treatment in 2005, >80 000 died [1]. Increased levels of inflammatory markers, such as elevated CRP, are a risk factor for cardiovascular events in both healthy people and in those with chronic kidney disease (CKD) [2]. CKD-associated mortality is also predicted by lower body mass index (BMI), the reverse of the relationship seen in the normal population [3]. In CKD, there is a well-recognized link between protein-energy wasting and inflammation, with the two conditions often coexisting [4] and reduced serum albumin predicts mortality [5]. However, the contribution of these two processes to disease outcome and the nature of the link between them is ill defined [5, 6]. One molecule that potentially links these two features is MIC-1/GDF15, a TGF-β superfamily cytokine.

MIC-1/GDF15 serum level, as documented by us, is a cardiovascular risk marker, which is independent of traditional risk factors, such as CRP [7]. MIC-1/GDF15, which is also known by a number of other synonyms [8], was first cloned on the basis of increased expression with

macrophage activation [9] and serum levels of MIC-1/GDF15 have clinical utility in diagnosis and prediction of disease course in chronic inflammatory [7, 10] and malignant diseases [11, 12]. We also recently identified MIC-1/GDF15 as a novel appetite regulator, which causes anorexia and weight loss when over-expressed in cancer [13]. In the same study, we demonstrated elevation of MIC-1/GDF15 in CKD with serum levels broadly comparable to patients with cancer-associated anorexia and weight loss [13]. In a separate healthy cohort, we have also demonstrated that serum MIC-1/GDF15 level is a predictor of longevity, independent of genetic background, age or BMI [14]. In view of the relationship of MIC-1/GDF15 to chronic inflammatory disease, its predictive value for atherosclerotic events, its role in disease-associated anorexia and weight loss and its prediction of mortality risk in healthy populations we sought to determine the relationship between MIC-1/GDF15 and altered nutritional status in CKD and the clinical utility of serum MIC-1/GDF15 measurement for predicting mortality in this disease. To study this, we have utilized two independent well-characterized cohorts of incident and prevalent dialysis patients.

Materials and methods

Patient cohorts

Patients were enrolled independently in the USA ($n = 381$) and Sweden ($n = 98$). Demographic information collected included age, sex, history of cardiovascular disease (CVD) and diabetes mellitus (DM) as well as height and weight. All patients had serum CRP (Dade Behring) and serum MIC-1/GDF15 determined on pre-dialysis blood samples as previously described [15].

Swedish patients represented a subset of incident dialysis patients enrolled in the dialysis program at the Karolinska University Hospital at Huddinge between 1997 and 2004 with an adequate volume of serum for MIC-1/GDF15 estimation. They are all included as participants in an ongoing prospective study, parts of which were previously described [16]. The glomerular filtration rate (GFR), as estimated by the mean of creatinine- and urea-clearance, was calculated from 24-h urinary samples. A competitive ELISA kit was used to measure the serum concentration of 8-hydroxy-2-deoxyguanosine (8-OH-dG) (Japanese Institute for the Control of Ageing, Fukuroi, Shizuoka, Japan). The remaining biochemical analyses (serum creatinine and serum albumin) were performed using routine methods at the Department of Clinical Chemistry at Karolinska University Hospital at Huddinge. Nutritional status was assessed by using the subjective global assessment (SGA) questionnaire [17]. This assessment was completed either at the time of, or within 1 week of, blood sample collection. BMI was calculated as weight (kg)/[height (m^2)]. Handgrip strength (HGS) was evaluated in both the dominant and non-dominant arms using the Harpenden Handgrip Dynamometer (Yamar, Jackson, MI). Lean body mass (LBM) was estimated by dual-energy X-ray absorptiometry using the DPX-L device (Lunar Corp., Madison, WI) and lean and fat components of BMI (LBMI and FBMI) were determined as previously described [18]. Patient exposure was censored for renal transplant ($n = 48$). Upon transplantation, patients were classified as alive from the time of study entry to transplantation and this served as the exposure time.

The US cohort consisted of 381 hemodialysis (HD) patients treated by chronic triweekly intermittent HD (IHD) for at least 30 days at outpatient dialysis units throughout Minneapolis—St Paul, MN, from April 1998 to March 1999. The patients studied were a sub-group of the original end-stage renal disease patient database reported previously [19]. Patient exposure was censored for renal transplant ($n = 18$), discontinuation of HD ($n = 1$) and transfer of patient to another renal dialysis unit ($n = 16$). These patients were classified as alive from the time of study entry to transplantation and this served as the exposure time classified as alive from the time of study entry to these events and this served as the exposure time. All patient studies were conducted with the patients' consent and approval from the respective institutional human ethics committee.

MIC-1/GDF15 enzyme immunoassay

Serum MIC-1/GDF15 was determined as previously described [15, 20]. We have investigated the analytical stability of MIC-1/GDF15 in serum and when stored at −70°C, there is no appreciable decrease in detectible analyte over prolonged periods (D. A. Brown and S. N. Breit, unpublished data).

Statistical analysis

Results are expressed as mean (SD), unless otherwise indicated, with $P < 0.05$ indicating significance. The relationship of MIC-1/GDF15 to SGA was investigated by logistic regression. Variables that were significantly associated with SGA or related to MIC-1/GDF15 were included in a multivariate logistic regression reporting odds ratios. To investigate correlations between other parameters and MIC-1, the Spearman's rank test was used as many values were not normally distributed. Examination of the difference in cumulative survival rates was compared between patients with varied MIC-1/GDF15 levels. Follow-up was computed from date of blood draw until date of death with censoring first for length of time interval of interest. In the Swedish and USA cohorts, renal transplant led to the patient being classified as censored and follow-up was calculated to time of transplant. Additionally, American patients transferred to another dialysis facility ($n = 16$) were classified as censored and follow-up calculated to time of transfer. Unadjusted and adjusted hazard ratios (HRs) of death and 95% confidence intervals (CIs) were estimated by use of Cox proportional hazard models. Adjusted HRs were estimated after first fitting models with variables identified in previous analyses as independent risk factors. Survival curves were computed by the Kaplan–Meier method and compared among risk stratification groups using the log-rank statistic. Analyses were done with STATA 11.0 software (StataCorp., College Station, TX) unless otherwise stated.

Results

Patient cohorts

Cohorts from the USA and Sweden had serum MIC-1/GDF15 levels estimated. Swedish patients were incident dialysis patients enrolled in the dialysis program at the Karolinska University Hospital at Huddinge between 1997 and 2004 [16]. The prevalent dialysis cohort from the USA comprised 381 consecutive HD patients enrolled for chronic IHD throughout Minneapolis—St Paul, MN [19]. Of the 98 Swedish patients (Table 1), 58 were males (59%), and the mean age was 53 years. Mean patient follow-up was 5.5 years (range 1.2–13.2 years), with a total of 36 deaths occurring during 319 patient-years of follow-up. A history of CVD and/or clinical signs of ischemic heart disease (angina pectoris) was present in 29 (30%) patients. DM was present in 28 (30%) of subjects, which was significantly less than in the cohort of patients from the USA ($P = 0.01$).

Table 1. Demographic and clinical measures in incident (Swedish) and prevalent (USA) dialysis populations

	USA	Sweden
Total	381	98
Age (years)	61 (16)	53 (13)
Sex		
Male	219 (57%)	58 (59%)
Female	162 (43%)	40 (41%)
DM	176 (46%)	28 (30%)
CVD	116 (30%)	29 (30%)
CRP (mg/L)	16.6 (24.9)	12.0 (20.3)
MIC-1/GDF15 (ng/mL)	8.3 (5.0)	8.4 (3.7)
BMI (kg/m^2)	25.3 (5.6)	24.9 (4.6)
Follow-up time (months)	19.4 (8.5)	66.4 (34.9)
Deaths	108 (28%)	36 (37%)
Yearly mortality rate	10.5% (5.7%)	3.2% (3.2%)

In the 381 prevalent dialysis patients from the USA, just over one half were male (58%) and the mean patient age was 61 years, which was significantly older than the Swedish population ($P < 0.01$). DM and a history of CVD were found in 46 and 30% of patients, respectively. The median number of years on dialysis was 2.0 years (range, 0.1–22 years). Mean patient follow-up was 1.6 years (range, 41 days to 3 years), with a total of 108 deaths occurring during 615 patient-years of follow-up. Key measurements of BMI, serum MIC-1/GDF15 level and CRP were not significantly different between the two populations ($P = 0.51$, 0.97 and 0.09, respectively). All patients with CKD had serum MIC-1/GDF15 levels above the normal range (0.2–1.2 ng/mL) [11]. The prevalent dialysis cohort had MIC-1/GDF15 serum levels ranging from 1.4 to 34.4 ng/mL (median = 7.1 ng/mL), which was not significantly different from the incident dialysis (Swedish) cohort (range, 3.0–25.1 ng/mL; median = 7.4 ng/mL).

Serum MIC-1/GDF15 is related to subjective global nutritional assessment in the Swedish Cohort

To study the nutritional changes associated with elevated serum MIC-1/GDF15 levels, we analyzed data from Swedish patients, from whom nutritional information was available. The SGA questionnaire [17] was used to assess nutritional status. The SGA nutritional index was segregated into normal (SGA = 1; $n = 69$) or abnormal (SGA > 1; $n = 27$) with data being unavailable in two patients. SGA was significantly related with BMI ($P = 0.02$) and HGS ($P = 0.01$) as well as serum creatinine ($P = 0.02$), serum MIC-1/GDF15 ($P = 0.02$). Patients with an abnormal SGA had higher serum MIC-1/GDF15 levels ($P < 0.01$; Mann–Whitney *U*-test). Serum MIC-1/GDF15 level was independently associated with SGA in multivariate logistic regression (Table 2). This model was further adjusted for factors that may be associated with MIC-1/GDF15 [age [21] ($P = 0.70$) and CRP [7] ($P = 0.01$)]. BMI and HGS are related to SGA assessment and they were therefore excluded from the multivariate logistic regression. This independent relationship of serum MIC-1/GDF15 levels to SGA, its role in weight regulation [13] and the prominent involvement of [7, 10] suggested that it would be of value to examine other factors that might be associated with serum MIC-1/GDF15 concentrations.

Serum MIC-1/GDF15 level is related to BMI and markers of inflammation/oxidative damage

Serum MIC-1/GDF15 levels were related to age ($\rho = 0.27$, $P < 0.01$), CRP ($\rho = 0.30$, $P < 0.01$), fibrinogen ($\rho = 0.34$, $P < 0.01$) and 8-OHdG ($\rho = 0.31$, $P < 0.01$) and serum albumin ($\rho = -0.21$, $P = 0.04$) (Table 3). While not significantly associated as a continuous variable in incident dialysis patients, serum MIC-1/GDF15 level above the median just failed to reach significant association with BMI ($P = 0.06$). However, patients with a serum MIC-1/GDF15 above the median were more likely to have a BMI <25 kg/m^2 ($P = 0.03$; chi-square analysis) consistent with the same relationship in the USA cohort previously published [13]. Many studies have indicated that reduced BMI and increased circulating markers of inflammation and oxidation are related to mortality in end-stage renal disease. Consequently, we sought to determine whether serum MIC-1/GDF15 level was also predictive of mortality in CKD patients starting renal replacement therapy.

Table 2. Multivariate logistic regression for SGA in the Swedish cohort

Variable	Odds ratio	95% CI	P
MIC-1/GDF15 (10 ng/mL)	4.84	1.09–21.62	0.04
CRP (1 g/L)	1.03	1.00–1.05	0.07
Serum creatinine (mg/dL)	0.99	0.99–1.0	<0.01
Age (1 year)	1.00	0.96–1.05	0.92

Serum MIC-1/GDF15 predicts mortality in incident dialysis patients

As shown in Figure 1, a MIC-1/GDF15 serum level above the median (7.4 ng/mL) was associated with a significantly increased mortality rate ($P = 0.01$). Over the nearly 14-year observation period, the survival rate was 53% for patients with serum MIC-1/GDF15 levels above the median compared with 73% for those patients with serum MIC-1/GDF15 levels below the median (Figure 1).

When serum MIC-1/GDF15 level was included in a multivariate analysis with age, sex, BMI, CRP, serum albumin, history of CVD or DM and GFR, MIC-1/GDF15 level was among the strongest independent predictors of mortality (HR = 4.48, $P = 0.02$; multivariate Cox proportional hazards). In this analysis CRP, serum albumin and BMI failed to be independently associated with mortality (Table 4). We next wished to determine if serum MIC-1/GDF15 levels were better at determining early or late events leading to mortality in renal failure. The adjusted (age, sex, GFR and history of CVD and/or DM) HR for death of patients with high serum MIC-1/GDF15 levels was only significant during the first 3 years following institution of dialysis [whole cohort, HR = 1.16 (1 ng/mL), 95% CI = 1.03–1.38; >1 year, HR = 1.16, 95% CI = 1.03–1.38; >2 years, HR = 1.08, 95% CI = 0.94–1.23; >3 years, HR = 0.98, 95% CI = 0.82–1.17; Figure 1]. Indeed, inclusion of the variables in Table 4 in a multivariate logistic regression revealed that MIC-1/GDF15,

Table 3. Factors correlated with serum MIC-1/GDF15 levels in the Swedish cohort

	Rho	P
Clinical parameters		
Age (years)	0.27	<0.01
GFR (mL/min)	−0.15	0.18
Nutritional markers		
Serum creatinine (mg/dL)	0.08	0.45
HGS (kg)	0.00	0.99
BMI (kg/m^2)	−0.07	0.52
Serum albumin (g/L)	−0.21	0.04
LBMI (kg)	0.06	0.58
FBMI (kg)	−0.11	0.33
SGA	0.28	0.01
Inflammatory and oxidation biomarkers		
CRP (mg/L)	0.301	<0.01
Fibrinogen (g/L)	0.343	<0.01
Ferritin (μg/L)	0.198	0.06
8-OHdG (ng/mL)	0.308	<0.01

along with history of DM and BMI, was independently predictive of mortality in the first 3 years after commencement of HD (P = 0.03, 0.02, 0.05, respectively). Having obtained these results, we sought to validate serum MIC-1/GDF15 measurement as a predictor of mortality in a second independent cohort of prevalent HD patients.

Serum MIC-1/GDF15 is a predictor of early mortality in end-stage renal disease in the USA cohort

In contrast to the Swedish cohort, the USA cohort had commenced dialysis treatment between 30 days and 22 years prior to MIC-1/GDF15 estimation. In this cohort, serum MIC-1/GDF15 level was also significantly correlated to dialysis vintage (days since dialysis started; DV) ($\rho = 0.18$, $P < 0.01$) and BMI ($\rho = -0.22$, $P < 0.01$). However, only BMI was independently correlated with MIC-1/GDF15 in multivariate regression analysis ($P < 0.01$) when included with DV.

Like the Swedish cohort, serum MIC-1/GDF15 level predicted mortality in prevalent HD patients (HR = 1.56, $P < 0.01$) (Table 4). Additionally, when serum MIC-1/GDF15 level was adjusted for age, sex, DV and history of CVD/DM, serum MIC-1/GDF15 remained an independent predictor of mortality at study completion (HR = 1.50, P = 0.02) (Table 4). Further adjustment for CRP and BMI attenuated the predictive power of MIC-1/GDF15 slightly (HR = 1.42, P = 0.06).

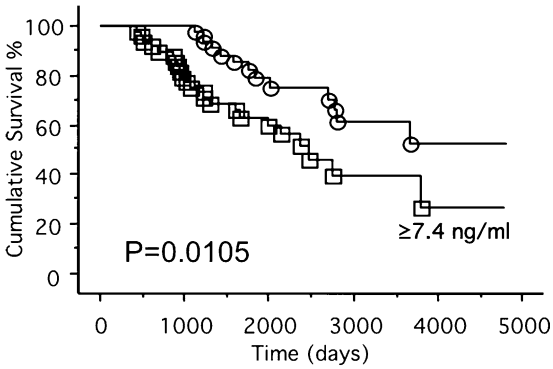

Fig. 1. Serum MIC-1/GDF15 level predicts mortality for renal replacement therapy. Kaplan–Meier plot of patients in the Swedish cohort ($n = 98$) were followed on dialysis from 1.2 to 13.2 years. Patients with serum MIC-1/GDF15 levels greater than the median 7.4 ng/mL had significantly higher mortality than patients with serum MIC-1/GDF15 levels below this level (P = 0.01).

Discussion

Elevated circulating markers of inflammation and reduced BMI are major predictors of mortality in advanced CKD [22]. Here, we show that in advanced CKD, serum MIC-1/GDF15 level is an additional novel predictor of mortality. Serum MIC-1/GDF15 is related to BMI, 8-OHdG and the nutritional measure SGA. This suggests that MIC-1/GDF15 might be a previously unrecognized link between oxidative stress, inflammation, reduced BMI and mortality in CKD.

The major limitations in this study are the use of incident and prevalent cohorts for the examination of MIC-1. Serum

Table 4. Multivariate Cox proportional hazard analysis of all-cause mortality in incident and prevalent dialysis patients

Variable	Adjustment	HR	95% CI	P
Swedish cohort ($n = 98$)				
MIC-1/GDF15 (10 ng/mL)				
1	Crude	2.91	1.15–6.72	0.02
2	1+ age, sex, GFR, CVD, DM	4.51	1.34–15.18	0.02
3	2+ serum albumin, CRP, BMI	4.48	1.22–16.47	0.02
Final model				
MIC (10 ng/mL)		4.48	1.22–16.47	0.02
Age (1 year)		1.13	1.06–1.21	<0.01
Sex (female)		1.88	0.71–4.93	0.20
DM (presence)		3.09	1.17–8.14	0.02
CVD (presence)		1.76	0.82–3.78	0.14
GFR (1 mL/min)		1.13	0.88–1.45	0.35
Serum albumin (1 g/L)		0.99	0.92–1.08	0.93
CRP (1 mg/L)		1.00	0.99–1.02	0.64
BMI (1 kg/m^2)		0.96	0.88–1.06	0.47
US cohort ($n = 381$)				
MIC-1/GDF15 (10 ng/mL)				
1	Crude	1.56	1.15–2.12	<0.01
2	1+ age, sex, DV, CVD, DM	1.50	1.07–2.11	0.02
3	2+ CRP, BMI	1.42	0.99–2.02	0.06
Final model				
MIC (10 ng/mL)		1.42	0.99–2.02	0.06
Age (1 year)		1.03	1.02–1.06	<0.01
Sex (female)		0.98	0.64–145	0.917
DM (presence)		1.52	1.01–2.29	0.05
CVD (presence)		1.21	0.79–1.83	0.38
DV (1 day)		1.0	1.0–1.0	0.02
CRP (1 mg/L)		1.11	1.05–1.17	<0.01
BMI (1 kg/m^2)		0.90	0.86–0.94	<0.01

MIC-1/GDF15 levels predicted death in the first 3 years of dialysis in the incident dialysis population. In contrast, the prevalent dialysis population had subjects on dialysis for periods of up to 22 years, possibly selecting for patients that tolerated dialysis well and attenuating the ability of serum MIC-1/GDF15 measurement to predict mortality. Indeed, further *post hoc* analysis of the prevalent dialysis cohort indicated that fully adjusted serum MIC-1/GDF15 levels significantly and independently predicted death in patients undergoing dialysis for $\leq$3 years at study completion ($n = 149$, HR 1.79, 95% CI 1.02–3.16). That similar relationships between serum MIC-1/GDF15 levels and mortality prediction could be defined in these very different cohorts potentially adds weight to the validity of the relationships defined in this study examining nutrition and mortality in CKD.

The relationship between BMI and mortality in CKD is the reverse of that in the normal population as reduced BMI is associated with increased mortality. Increased mortality with decreasing BMI has also been defined in the elderly [3] as well as in patients with cancer [3, 13], rheumatoid arthritis [3] and cardiac failure [3]. Each of these conditions, like CKD, is associated with relatively elevated serum MIC-1/GDF15 levels [10, 13, 21, 23]. Cardiac failure patients with serum MIC-1/GDF15 levels in the top quartile are known to have a significantly increased risk of mortality independent of all other known factors and also have a significantly lower BMI [23]. In cancer-associated cachexia, serum MIC-1/GDF15 levels correlate with weight loss [13]. Moreover, administration of MIC-1/GDF15 to animals leads to significant weight reduction and modification of hypothalamic satiety signals in a manner similar to, but distinct from leptin [13].

Leptin is an important appetite regulator and like other adipokines, its serum levels are elevated in CKD and have been linked with mortality risk. However, as with BMI, the association between leptin serum levels and mortality is reversed in CKD patients when compared with healthy populations [24]. Similarly, in normal populations, low adiponectin serum levels associate with increased mortality and the reverse is true in CKD [25]. As adipose tissue is a major source of leptin and influences adiponectin serum levels, altered levels of these two adipokines may simply reflect reduced total fat mass, which is associated with higher mortality in CKD [6]. This cannot be the case for MIC-1/GDF15. Like leptin, MIC-1/GDF15 acts directly upon the hypothalamus to reduce food intake and reduce energy expenditure [13]. However, unlike leptin, serum MIC-1/GDF15 levels increase with decreasing BMI and elevated serum MIC-1/GDF15 levels predict mortality in CKD as well as healthy populations independently of genetic factors [7, 14, 26].

Patients with CKD often have protein-energy wasting associated with significant inflammation as determined by elevated circulating inflammatory markers and markers of oxidative stress [27], which in our study are reflected by an elevation in serum CRP and 8-OHdG levels, respectively. Cellular responses to oxidative damage include upregulation of p53 expression, which may induce cell cycle arrest and limit genotoxicity [28]. An activated p53 pathway is relevant to end-stage renal disease [29] and is also a major regulator of MIC-1/GDF15 expression [30]. Oxidative damage is thought to mediate chronic inflammatory states that are seen in advanced CKD patients [31] and the capacity of MIC-1/GDF15 to reflect this effect is suggested by the relationship of its serum levels with circulating levels of 8-OHdG. As 8-OHdG levels were not available on both cohorts, we were not able to verify the relationship of MIC-1/GDF15 with measures of oxidative stress in patients who had commenced dialysis or whether reduced oxidative stress in these patients contributed to lower serum MIC-1/GDF15 levels in this cohort.

Oxidative stress, increased inflammation and MIC-1/GDF15 are linked with atherosclerotic disease, a major component of all-cause mortality in CKD [32]. Mortality in CKD is strongly linked to decreasing BMI, anorexia and hypoalbuminemia, which are also the strongest predictors of cardiovascular death in CKD [6]. As MIC-1/GDF15 is significantly related to these factors and predicts mortality independently of a history of atherosclerotic disease as well as being independently related to atherosclerotic events [7], reduction of circulating MIC-1/GDF15 concentrations may lead to decreased mortality. Based on the evidence presented here, while highly speculative, MIC-1/GDF15 may play a role in mediating the consequences of inflammation and oxidative stress, directly linking them to regulation of weight. Weight loss mediated by MIC-1/GDF15 can be reversed or prevented by the administration of specific anti-MIC-1/GDF15 neutralizing antibodies in animal models [13]. This finding raises the possibility that reducing circulating serum MIC-1/GDF15 concentrations in CKD may improve appetite, if not also impacting positively on mortality.

In conclusion, we have generated significant preliminary data demonstrating the predictive value of serum MIC-1/GDF15 level estimation as a prospective marker of all-cause mortality in both incident and prevalent dialysis patients. MIC-1/GDF15 serum level determination appears to enhance the prediction of mortality in the first 3 years of dialysis beyond that afforded by the consideration of age, BMI, CRP, history of DM and IHD as well as time on dialysis. Additionally, MIC-1/GDF15 is correlated with 8-OHdG and other inflammatory markers [7] and appetite [13]. Therefore, MIC-1/GDF15 could represent a previously unrecognized mediator of inflammation, oxidative stress and anorexia in CKD whose levels could be reduced by therapeutic antibodies, if this approach was sufficiently supported by future studies. The incidence of CKD is steadily rising [1] and the demand for renal transplantation continues to exceed organ availability, leading to significant morbidity and mortality in dialysis patients waiting for transplantation [33]. Clearly, the ability to identify those patients who will not tolerate HD for long periods offers a way to rationalize the allocation of organs. The reliance on transplantation to reduce the risk of mortality in end-stage renal disease might also be diminished if the risks associated with long-term dialysis could be reduced. Consequently, the confirmation of the predictive power of MIC-1/GDF15 in appropriately designed prospective studies should be undertaken. Additionally, the modulation of MIC-1/GDF15 as a therapeutic mode to reduce cachexia and possibly mortality in end-stage renal disease could be considered.

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Conflict of interest statement. D.A.B. and S.N.B. are inventors on patents filed by St Vincent's Hospital, which pertain to the use of MIC-1/GDF15 in disease. Dr F.A. consults for several *in vitro* diagnostics companies that manufacturer assays to detect cardiovascular biomarkers. The remaining authors declare no conflict of interest.

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