Association between proteinuria and left ventricular mass index: a cardiac MRI study in patients with chronic kidney disease

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Abstract

Background. Chronic kidney disease (CKD) is associated with increased cardiovascular morbidity and mortality. We hypothesized that the level of proteinuria would correlate with left ventricular mass, providing a potential link between elevated protein excretion, left ventricular hypertrophy (LVH) and the increased mortality seen in patients with CKD. In order to do this, we assessed the determinants of left ventricular mass, measured using cardiac magnetic resonance (CMR) imaging, in patients with CKD.

Methods. Patients attending the renal clinic with CKD stages 2–4 and diabetic nephropathy (n = 26) and IgA nephropathy (n = 23) were recruited. They underwent detailed demographic, biochemical and vascular phenotyping and CMR imaging. Proteinuria was measured using spot protein:creatinine ratio (PCR). Left ventricular mass index (LVMI) was calculated from short-axis cine imaging using Argus software and adjusted for body surface area.

Results. Log-PCR correlated significantly with LVMI, as did waist circumference, pulse pressure and systolic blood pressure. LVMI was higher in men. When these variables were entered into a linear regression model, log-PCR (P = 0.006) and systolic blood pressure (P < 0.001) independently predicted LVMI. Renal function was not associated with LVMI.

Conclusions. Using volume-independent CMR imaging, we have demonstrated that the level of urinary protein excretion is independently and significantly associated with left ventricular mass in patients with CKD. This relationship was independent of blood pressure. This finding provides a novel link between CKD and increased cardiovascular risk.

Keywords: cardiac MRI; cardiovascular; CKD; LVH; proteinuria

Introduction

Left ventricular hypertrophy (LVH) is a predictor of cardiovascular and all-cause mortality in patients with hypertension and patients with chronic kidney disease (CKD) [1,2]. Reduction of LV mass has been associated with reduced mortality [3] in a variety of groups at high cardiovascular (CV) risk. Patients with CKD have increased CV risk, above that of the general population, which increases as renal function declines [4]. However, the mechanisms responsible for this increased risk remain poorly elucidated, with the majority of interest focussing on patients with end-stage renal disease. In patients receiving maintenance haemodialysis, we have shown systolic blood pressure to be the main determinant of LVH [5].

In patients with CKD, the level of proteinuria is both the most accurate predictor of renal outcome [6,7] and an independent predictor of mortality [8]. In patients without overt renal disease, a graded relationship has been shown to exist between proteinuria and mortality risk in a diverse range of populations [9–13]. The presence of microalbuminuria has also been shown to be predictive of LVH in patients with essential hypertension using echo [14,15] and electrocardiogram (ECG) criteria [16] and also in patients with diabetes [17] without overt nephropathy.

The relationship between proteinuria and left ventricular mass index in patients with chronic kidney disease is, however, unclear. We hypothesized that the level of proteinuria would correlate with left ventricular mass in patients with CKD, providing a potential link between elevated protein excretion, LVH and the increased mortality seen in these patients. In order to do this, we assessed the determinants of left ventricular mass index (LVMI), measured using cardiac magnetic resonance (MR) imaging [5] in patients with diabetic and non-diabetic CKD.

Materials and methods

Study design, setting, participants

In a cross-sectional cohort study, we consecutively recruited adult patients with either diabetic nephropathy or biopsy-proven IgA nephropathy and CKD stages 2–4 (n = 49) from renal clinics in the West of Scotland. Patients receiving immunosuppression, had active infection or who were unable to undergo cardiac magnetic resonance (CMR) scanning
were excluded. There was no proteinuria cut-off in order to enable assessment of a broad range of values. Patients with CKD stages 2–4 were included in order to assess the effect of established renal impairment not yet requiring renal replacement therapy on LVMI. The protocol was approved by the local research ethics committee, and all patients gave written informed consent.

Patients attended the Glasgow Clinical Research Facility and underwent baseline investigations. Renal function was calculated using the four-variable Modification of Diet in Renal Disease (MDRD) formula, proteinuria was measured using a spot protein:creatinine ratio (PCR), and 24-h proteinuria quantification (24 h QP). The lowest of three office blood pressure measurements, whilst taking prescribed medications, was recorded. Waist circumference, haemoglobin, bone biochemistry including parathyroid hormone (PTH), 24-h urinary sodium and C-reactive protein (CRP) were measured. Carotid-femoral pulse wave velocity was recorded using the SphygmoCor Vx system and the average of three readings taken.

Cardiac magnetic resonance imaging scanning

Non-contrast CMR was performed to determine LVMI using short-axis cine slices from a 1.5-Tesla Siemens (Erlanger) cardiac magnetic resonance imaging (MRI) scanner as previously described [5]. Briefly, long-axis pilot scans were obtained through the apex of the left ventricle, aligning it with the centre of the mitral valve, and then serial 8-mm-thick short-axis images were obtained. A fast imaging with steady-state precession (FISP) sequence was then used to acquire cine images in long-axis planes (vertical long axis, horizontal long axis, LV outflow tract) followed by sequential short-axis LV cine loops (8-mm slice thickness, 2-mm gap between slices) from the anteroventricular ring to the apex. Slices were contiguous. Imaging parameters, which were standardized for all patients, included repetition time/echo time/slab thickness/field of view of 3.14 ms/1.6 ms/60°/22.1, 1.3, 8.0 mm/340 mm. LVM was analysed by a blinded observer from short-axis cine loops using manual tracing of epicardial and endocardial end-systolic and end-diastolic contours. End-systolic volume (ESV), end-diastolic volume (EDV) and LVM were calculated using analysis software (Argus; Siemens). Values were adjusted for body surface area (Mosteller formula, BSA (m²) = √((weight (kg) × height (cm))/3600)), and LVH was defined as LVMI > 84.1 g/m² for men and >76.4 g/m² for women; LV systolic dysfunction was defined as LV ejection fraction (LV EF) <55% [18].

**Table 1.** Baseline cohort demographics—whole cohort and split by primary renal disease

<table>
<thead>
<tr>
<th></th>
<th>All (n = 49)</th>
<th>DMN (n = 26)</th>
<th>IgAN (n = 23)</th>
<th>DMN vs. IgAN (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>57.1 (47.1–66.1)</td>
<td>64.8 (47.5–75.1)</td>
<td>54.0 (43.0–59.6)</td>
<td>0.022*</td>
</tr>
<tr>
<td>% Male</td>
<td>73.5%</td>
<td>65.4%</td>
<td>82.6%</td>
<td>0.15</td>
</tr>
<tr>
<td>eGFR (mL/min)</td>
<td>38.1 ± 21.0</td>
<td>33.8 ± 19.1</td>
<td>42.0 ± 22.2</td>
<td>0.199</td>
</tr>
<tr>
<td>Waist circ (cm)</td>
<td>100.9 ± 13.0</td>
<td>104.9 ± 12.0</td>
<td>96.4 ± 13.0</td>
<td>0.029*</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.1 ± 4.8</td>
<td>30.3 ± 4.1</td>
<td>28.1 ± 5.3</td>
<td>0.188</td>
</tr>
<tr>
<td>PWV (ms⁻¹)</td>
<td>10.2 ± 3.6</td>
<td>11.8 ± 3.5</td>
<td>8.1 ± 2.6</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>12.5 ± 1.6</td>
<td>12.0 ± 1.4</td>
<td>13.0 ± 1.6</td>
<td>0.031*</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>145.7 ± 21.0</td>
<td>153.6 ± 18.0</td>
<td>136.8 ± 20.9</td>
<td>0.004*</td>
</tr>
<tr>
<td>LVM (g/m²)</td>
<td>84.8 ± 20.0</td>
<td>82.5 ± 18.0</td>
<td>85.6 ± 21.0</td>
<td>0.186</td>
</tr>
<tr>
<td>% LVM</td>
<td>53%</td>
<td>69.2%</td>
<td>76.6%</td>
<td>0.016*</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>69.9 ± 8.9</td>
<td>71.2 ± 7.6</td>
<td>68.5 ± 10.2</td>
<td>0.305</td>
</tr>
<tr>
<td>PCR (mg/mmol)</td>
<td>82.5 (23.3–236.4)</td>
<td>121 (21.5–319)</td>
<td>48 (24–172)</td>
<td>0.163</td>
</tr>
<tr>
<td>24 h QP (g/24 h)</td>
<td>0.7 (0.3–2.6)</td>
<td>1.9 (0.5–4.1)</td>
<td>0.6 (0.3–1.8)</td>
<td>0.048*</td>
</tr>
<tr>
<td>Urinary sodium (mmol/24 h)</td>
<td>164.9 ± 63.5</td>
<td>177.2 ± 65.1</td>
<td>150.2 ± 52.3</td>
<td>0.153</td>
</tr>
<tr>
<td>Number of antihypertensives</td>
<td>2.7 ± 1.4</td>
<td>2.8 ± 1.5</td>
<td>2.5 ± 1.2</td>
<td>0.54</td>
</tr>
<tr>
<td>% Prescribed antihypertensives</td>
<td>96%</td>
<td>92%</td>
<td>100%</td>
<td>0.222</td>
</tr>
<tr>
<td>% Prescribed RAS inhibition</td>
<td>83.7%</td>
<td>80.8%</td>
<td>87.0%</td>
<td>0.424</td>
</tr>
<tr>
<td>% Current smokers</td>
<td>12.2%</td>
<td>7.7%</td>
<td>17.4%</td>
<td>0.45</td>
</tr>
<tr>
<td>% History of vascular disease</td>
<td>22.5%</td>
<td>30.8%</td>
<td>13.0%</td>
<td>0.127</td>
</tr>
</tbody>
</table>

Mean ± SD or median (IQR). Comparison made by *t*-test, Mann–Whitney *U*-test or chi square as appropriate. *P < 0.05, significant result. y, years; eGFR, estimated glomerular filtration rate, measured using the MDRD4 formula; Waist circ, waist circumference; BMI, body mass index; PWV, carotid-femoral pulse wave velocity; Hb, haemoglobin; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; LVM, left ventricular mass index; LVM, left ventricular hypertrophy; LVEF, left ventricular ejection fraction; PCR, protein:creatinine ratio; 24 h QP, 24 h quantified proteinuria.

**Statistical analysis**

Statistical analysis was carried out using SPSS (Illinois) version 15.0. Data were plotted to determine normality and are expressed as mean ± SD or median and interquartile range. Parametric correlations were calculated using Pearson’s correlation, non-parametric using Spearman’s. Variables were log transformed to obtain a normal distribution as required. Linear regression was used to assess the relationship between continuous variables.

**Results**

**Demographics**

Twenty-six patients had diabetic nephropathy (DMN), and 23 had IgA nephropathy (IgAN); 73.5% (n = 36) were male (Table 1); 22.5% had a history of vascular disease, and 12% were current smokers. The median age was 57.1 (IQR 47.1–66.1) years; mean estimated glomerular filtration rate (eGFR) 38.1 (21.0) mL/min; median PCR 82.5 (23–236) mg/mmol; median 24 h QP 0.7 g/24 h (0.3–2.6). Mean Hb was 12.5 (1.6) g/dL; mean body mass index (BMI) 29.1 (4.8) kg/m², systolic blood pressure (SBP) 145.7 (21.0) mmHg, diastolic blood pressure (DBP) 81.4 (10.4) mmHg, and the mean number of antihypertensive agents was 2.7 (range 0–6). Mean time from diagnosis was 3.7 years, and study participants are representative of the population with these primary renal diseases seen in the West of Scotland [19,20]. Of patients, 83.7% were prescribed renin-angiotensin system (RAS) inhibitors. Only one patient had nephrotic syndrome, one patient was taking a phosphate binder, and five were prescribed an erythropoietin supplementing agent. No patients were taking a vitamin D analogue. Mean LV mass index was 84.8 g/m² (SD20.0). Fifty-three per cent of patients had LVH; mean ejection fraction was 69.9% (8.9)
All patients who entered the study completed it and were analysed.

**Correlations with LVMI**

Log-PCR was correlated with LVMI ($r^2 = 0.515, P = 0.001$; Figure 1a), as was 24h QP ($r^2 = 0.477, P = 0.001$), waist circumference ($r^2 = 0.355, P = 0.017$), pulse pressure ($r^2 = 0.594, P < 0.001$) and systolic blood pressure ($r^2 = 0.621, P < 0.001$ Figure 1b). LVMI was higher in men ($P < 0.001$) and lower in patients prescribed RAS inhibition (81.4 vs. 96.1 g, $P = 0.046$). Haemoglobin, eGFR (Figure 1c), number of anti-hypertensives, age, pulse wave velocity, calcium phosphate product, PTH, smoking history, CRP, urinary sodium excretion, primary renal disease and diastolic blood pressure did not correlate with LVMI.

When the subgroups with DMN or IgAN were analysed individually, the relationship with sex, RAS usage, proteinuria, systolic blood pressure, pulse pressure and waist circumference persisted, and those variables which were not significantly associated, including eGFR, remained so.

**Determinants of LV mass**

All significantly associated variables were entered into a univariate linear regression model, using LVMI as a continuous variable, with SBP used as the most highly correlated measure of blood pressure and PCR as the most highly correlated measure of proteinuria (Table 2). Entering the variables in a backward stepwise regression, 58% of the variation in LV mass is explained ($P < 0.001$). The importance of proteinuria and systolic blood pressure in explaining the variance in LV mass (Table 3) was confirmed, with proteinuria accounting for 22.8% and systolic blood pressure 28.7%. Primary renal diagnosis, when entered into the model, was not an independent predictor of LVMI; nor was waist circumference, sex or RAS usage. When 24h QP was entered into the multivariate model instead of PCR, the results were unaffected ($P = 0.007$ for 24 h QP).

Looking at patients with diabetic nephropathy alone, the model persisted; however for patients with IgA nephropathy alone, although blood pressure control was better, only systolic blood pressure remained a positive predictor in multivariate linear regression.

**Discussion**

Existing studies of LVH in renal disease have used echocardiography or ECG. The dependence of echocardiography on intravascular volume leads to overestimation of LVMI in patients with advanced renal disease [21], and whilst ECG criteria can be applied, this is generally less reliable [22]. This study is the first to demonstrate, using volume-independent cardiac MR imaging, that the level of urinary protein excretion is independently and significantly associated with left ventricular mass in patients with CKD. This relationship was strongest in patients with diabetic kidney disease and is independent of blood pressure.
Studies using echocardiography [22,23] have found a stepwise increase in the prevalence of left ventricular hypertrophy with declining renal function (CKD stages 1–4). Despite LVH being present in half of our patients with moderately impaired renal function, estimated glomerular filtration rate was not significantly associated with myocardial mass. The MESA study [24] looked at the association of LVMI, using CMR, and renal function in patients with primary atherosclerotic disease with concomitant reduced eGFR and found a non-linear association with renal function, whereby LVH was associated with a GFR between 60 and 75 mL/min but no association above 75 mL/min or below 60 mL/min once adjustment was made for blood pressure. It is clear that LV mass increases significantly by the time a patient starts dialysis [25], and it may be that changes in the left ventricle occur early in the course of renal disease, in association with the development of hypertension and mild fluid overload, and then further significant changes occur with more marked renal impairment, in the pre-dialysis phase, in association with disturbances in bone metabolism and other uraemic factors [5].

Other studies examining the relationship between LVMI and renal function have used ECG criteria [26], which are recognized to be inaccurate [21]. The role of proteinuria in determining LV mass has been explored by other investigators. The MONICA/KORA study [27] demonstrated using echo that albuminuria, even at low levels, was a significant predictor of LVMI. Paoletti et al. [28] recruited 244 patients with non-diabetic kidney disease stages 1–5 and calculated LV mass using echo and proteinuria with 24 h collection. In the regression model, LVMI was associated only with pulse pressure, proteinuria and duration of hypertension. When only patients with CKD 3–5 were considered, LVMI was associated with pulse pressure and age only—the association with proteinuria was lost. Therefore, their findings in non-diabetic patients are consistent with our mixed cohort, where the significant independent predictors of LVMI are blood pressure and proteinuria; however, contrary to our findings, in their study the association with proteinuria did not persist at lower levels of renal function, which may be a reflection of the modality used to assess LVMI. Using ECG Cornell voltage criteria, Nobakhtaghigi et al. [28] found an association between urinary albumin excretion, LVM and mortality, which they postulate may be due to diffuse microvascular injury. These are intriguing findings, although the generalizability to patients with chronic kidney disease, both diabetic and non-diabetic, is uncertain.

The association of LV mass with blood pressure seen in our cohort is as would be expected in terms of increased afterload. Of interest, the lack of association of LVMI with carotid-femoral pulse wave velocity raises uncertainty about the role of increased arterial stiffness leading to increased afterload in CKD. However, the association with pulse pressure suggests that perhaps fluid overload has more of a role to play.

In this study, we have extended findings from previous investigators by confirming the independent association of proteinuria and left ventricular mass using the gold standard measure of LVM, cardiac MR, in patients with CKD stages 2–4. Small patient numbers limit individual disease subgroup analysis; therefore, differences between diseases must be interpreted with caution as they may reflect under-powering of the study or differences between primary and secondary renal diseases.

The association with obesity is an important and interesting finding, and it may be that part of the association seen between proteinuria and LVMI in this cohort is related to the high prevalence of obesity, which is known to be associated with proteinuria [29]. Adipohormones such as adiponectin, leptin and resistin, released predominantly from adipose tissue, have been shown to have proliferative effects on smooth muscle cells whilst increasing vascular stiffness [30], and also an association has been demonstrated between adiponectin and left ventricular mass index [31]. The impact of obesity, however, does not fully explain the relationship, as when entered into the linear regression model proteinuria remained a significant predictor of LVMI, whilst waist circumference did not.

Although the identified predictors of LVMI are largely traditional and account for 61% of the variation in LVMI in patients with CKD, it remains unexplained why proteinuria should predict LVMI. Previously, it was thought that albuminuria reflected generalized endothelial dysfunction [32]. Our findings of an association of total proteinuria with left ventricular mass suggest this may not be the only explanation. Hypertension, renal-specific factors such as reninase [33] or elevated aldosterone, underlying levels of inflammation, sodium and water retention, an association with more marked endothelial dysfunction, the pro-coagulant state or oxidative stress may be involved, resulting in vascular leakage and ventricular hypertrophy or diffuse fibrosis. Similarly, an unidentified renal marker or genetic predisposition may have a role. An alternative explanation may be that elevated left ventricular mass drives proteinuria, perhaps via natriuretic peptides [34].
Previous investigators have identified an association between carotid-intima-media thickness and urinary albumin excretion, suggesting that there might be systemic vascular changes associated with proteinuria [26]. Diabetic nephropathy is recognized to be a condition with systemic endothelial dysfunction and marked activation of the renin–angiotensin–aldosterone system, whereas IgA nephropathy is a more renal-limited condition, and mechanisms of proteinuria production between the two diseases differ, perhaps explaining the differing subgroup results.

In patients with chronic kidney disease, the use of total proteinuria encompasses both glomerular and tubular dysfunction. Also, the use of a protein:creatinine ratio removes the inaccuracies associated with a 24-h collection. In our cohort, PCR correlated more highly with LVMl and was therefore used for the primary analysis; however, using 24h QP did not alter the results. Direct measurement of albumin excretion was not available in this cohort and would have been interesting to compare with total proteinuria, as one would expect albuminuria to be more closely correlated if the association with LVMl was purely mediated by endothelial dysfunction. It would also be interesting to expand the study to include patients with milder CKD and proteinuria, as increases in LVMl have been seen in patients with preserved renal function and biopsy-proven glomerulonephritis [35] or adult polycystic kidney disease [36], but the relationship to proteinuria is unclear. Including larger numbers of patients at the extremes of proteinuria measurement would also enhance understanding of whether there exists a threshold or stepwise effect of proteinuria.

As a cross-sectional analysis, this study cannot assume causality, and indeed we do not have prognostic data relating to the cardiovascular morbidity and mortality. Using estimated GFR rather than direct measurement will introduce some inaccuracy, although the MDRD4 formula is well validated in patients with CKD. There are baseline differences between the two groups, reflecting their primary medical conditions; however, the baseline differences are unlikely to have influenced the study findings. We chose to assess patients with IgA nephropathy because it is the commonest primary glomerulopathy seen in our population; however, this study should be extended to include patients with other primary glomerulopathies.

In conclusion, proteinuria is significantly and independently associated with left ventricular mass index in patients with chronic kidney disease. This association could go some way to explaining why studies such as the RENAAL study [37–39] failed to demonstrate a protective role for renin–angiotensin blockade in terms of cardiovascular death or myocardial infarction, whilst still protecting the kidney, unless proteinuria was reduced. The findings from this study are intriguing and should prompt further study into the association between proteinuria and LVMl in patients with CKD, both primary and secondary, and suggest that future studies should focus also on left ventricular mass and its regression in patients with chronic kidney disease and proteinuria.

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p-Cresyl sulphate and indoxyl sulphate predict progression of chronic kidney disease

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Abstract

Background. Indoxyl sulphate (IS) and p-cresyl sulphate (PCS) are uremic toxins that have similar protein binding, dialytic clearance and proinflammatory features. However, only a few prospective studies have evaluated possible associations between these two retained solutes...