Prevalence and associations of limited health literacy in chronic kidney disease: a systematic review

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Abstract

Background. Health literacy (HL) is important in chronic disease. This review aimed to evaluate the literature evidence on prevalence and associations of limited HL in chronic kidney disease (CKD).

Methods. Seven databases were searched using terms for CKD and HL. Studies were included that ascertained the prevalence of limited HL using a validated tool in adults with CKD of any stage. The primary outcome was an objectively measured prevalence of limited HL in a population with CKD. The secondary outcome was associations of limited HL. Two reviewers assessed study inclusion and quality. Prevalence values were combined using a random-effect model to give overall prevalence.

Results. Eighty-two studies were identified from searching, of which six met the inclusion criteria. The total number of people in all studies was 1405. Five studies were in dialysis or transplant populations, and all were from the USA. There was a significant heterogeneity in the prevalence of limited HL [9–32% (median 25%, inter-quartile range 16%)]. The pooled prevalence of limited HL in all studies was 22.7% (95% confidence interval 20.6–24.8%), but study heterogeneity limited the generalizability of this combined prevalence. The review identified associations between limited HL and socio-economic factors (lower education attainment, lower income), and certain process and outcome measures (lower likelihood of referral for transplant, higher mortality).

Conclusions. Limited HL is common among people with CKD and independently associated with socio-economic factors and health outcomes. It may represent an important determinant of inequality in CKD.

Keywords: chronic kidney disease; health literacy; inequalities; prevalence

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Introduction

Chronic kidney disease (CKD) is an important, prevalent and growing problem. In the UK, the 2010 Health Survey for England estimated that ~6% of men and 7% of women have Stage 3–5 CKD and that the prevalence increased with age to 29% of men and 35% of women over 75 [1]. In the USA, the National Health and Nutrition Examination Survey (NHANES) estimated a crude prevalence of CKD of ~17% of the adult population [2]. CKD is strongly associated with the metabolic syndrome, obesity, diabetes, hypertension and cardiovascular disease, and most people with CKD are at greater risk of developing cardiovascular disease than of progression to end-stage kidney disease (ESKD) [3–5]. Though only a small proportion of people with CKD progress to ESKD [6, 7], renal replacement therapy (RRT—dialysis and transplant) represents a large burden of care and cost to health services [8].

Self-management and shared decision-making are important aspects of complication prevention for people with CKD, with emerging evidence of their role in determining certain CKD outcomes [9, 10]. Achieving a degree of understanding of the condition is an important component of self-management and shared decision-making that may contribute to improved outcomes, as has been suggested for other chronic conditions [11]. Factors such as medication adherence (to achieve blood pressure control, reduction in proteinuria and, where relevant, diabetes control), avoiding potentially nephrotoxic substances (such as non-steroidal anti-inflammatory drugs), attending monitoring appointments and avoiding adverse behaviours (such as smoking, high dietary salt intake, and lack of exercise) may all be influenced by patient understanding and play a part in reducing the risk of progression and development of complications in CKD [12].

Health inequalities related to age, gender, socio-economic status and ethnicity have been recognized throughout the CKD pathway, including the prevalence of risk factors (e.g. diabetes), prevalence of CKD, risk of progression and RRT [13]. There is evidence of greater prevalence of CKD in women, older people [1, 2] and lower socio-economic groups [14–16], and advanced CKD (Stages 3b, 4 and 5) varies by ethnicity [17, 18]. There is also some evidence of more rapid progression in people from more deprived backgrounds and in certain ethnic groups [19–23].

In the UK, there have been recent improvements in the standardization of care of CKD through the Quality and Outcomes Framework (which incentivises general practitioners to keep registers of patients with CKD Stage 3 and above and to provide certain standards of care). However, little is known about inequalities in health-care process and outcome for people with CKD and the contribution of suboptimal self-management and shared decision-making to clinical outcomes [24].

There is considerable evidence that an adequate level of health literacy (HL) (defined as ‘the cognitive and social skills which determine the motivation and ability of individuals to gain access to, understand, and use information in ways that promote and maintain good health’) [25] is important to the disease management process and that inadequate HL is a potentially modifiable determinant of poor health outcomes and of health inequalities in people with chronic disease [26–29]. This has been increasingly recognized with CKD, though to date, considerably more evidence exists for the role of HL in other chronic diseases such as diabetes [27, 30, 31]. The European health policy has recognized the inter-related roles of HL, self-management and shared decision-making in the management of chronic conditions and reduction in inequalities in outcome [32].

The aim of this review was to synthesize and critically appraise the literature evidence on the prevalence and associations of limited HL in CKD.

Materials and methods

We aimed to identify studies which had measured HL in people with CKD and recorded a prevalence of limited HL (defined as ‘low’, ‘inadequate’ or ‘marginal’ HL; Table 1). The specific outcomes of interest were an objectively measured prevalence of limited HL in a population with CKD, the measure by which that level of HL was obtained and the associations of limited HL. The indices most frequently used include the Rapid Estimate of Adult Literacy in Medicine (REALM) and derivatives, the Test of Functional Health Literacy in adults (TOFHLA) and derivatives (including the short form, STOFHLA), the Short Assessment of Health Literacy for Spanish-speaking Adults (SAHLSA) and the Newest Vital Sign (NVS). A summary of these measures is given in Table 1. In view of the differences between STOFHLA and TOFHLA in terms of the average duration of time to complete them and the number of items, they were considered separately, but REALM derivatives (seeking correct pronunciation of disease-specific words) were considered together because the basic structure of the tool was the same.

The exposure of interest was a diagnosis of CKD, and studies investigating any stage of CKD were included. We included cross-sectional, cohort and randomized controlled study designs that contained a cross-sectional or baseline assessment of the proportion of people with limited HL in order to derive prevalence. We chose a minimum study population of 50 participants in order to identify studies with a predominantly quantitative rather than qualitative focus and restricted the age to adults over 18 years. We included only studies that measured HL using a validated measurement tool.

Database searching was conducted in February 2012. The databases searched were as follows: Medline (1996 onwards), Health Management Information Consortium (HMIC, 1979 onwards), Embase (1980 onwards), Cinahl (1981 onwards), Ovidfulltext (including Psycharticles), Psychinfo (1995 onwards) and the British Education Index (BEI). Searching was undertaken using the Wolters Kluwer OvidSP gateway for the Medline, HMIC, Embase, Cinahl, Ovidfulltext and Psycharticles searches. The Psychinfo and BEI searches were undertaken directly via their Internet access portals.

Search terms were used for HL and CKD. HL terms were drawn from a previous review of prevalence of HL, updated with more recent HL measures [33]. CKD terms were drawn from renal reviews identified through the Cochrane Renal Group website [34].

Terms used were as follows: health, literacy, numeracy, health literacy, TOFHLA, Rapid Estimate of Adult Literacy in Medicine, REALM and read, Wide Range Achievement Test, WRAT, Slosson oral reading test, SORT AND read, Peabody Individual Achievement Test, PIAT, National Adult Reading Test, NART, AMNART, Woodcock-Johnson AND test, medical terminology AND achievement, MART AND read, literacy assessment for diabetes, and adult basic education test, Newest Vital Sign, NVS, STOFHLA, SAHLSA, Short Assessment of Health Literacy for Spanish Speaking Adults. These terms were searched as title, abstract or keyword. They were searched against chronic disease terms for CKD (renal disease, kidney disease, kidney failure chronic, chronic kidney failure, and chronic renal failure).

CKD, CRF, renal replacement therapy, haemodialysis, haemodialysis, renal transplant, peritoneal dialysis, end-stage renal disease, end-stage renal failure, end stage kidney disease, ESKD, ESRD, ESRF). We also hand searched reference lists of review articles and included studies, and
Prevalence and associations of HL in CKD

Table 1. Common HL measures

<table>
<thead>
<tr>
<th>Instrument</th>
<th>How administered</th>
<th>Description</th>
<th>Approximate time taken to complete</th>
<th>Scoring</th>
<th>Categorization of health literacy status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid Estimate of Adult Literacy in Medicine (REALM)</td>
<td>Interview</td>
<td>Assessing correct pronunciation of 125 words from primary care materials (the more commonly used short form is 66 words). Points allocated for correct pronunciation of each word.</td>
<td>3–5 min</td>
<td>Score between 0–66 converted to US school grade</td>
<td>0–44: inadequate HL, 45–60: marginal HL, 61–66: adequate HL</td>
</tr>
<tr>
<td>Short Assessment of Health Literacy for Spanish-speaking Adults (SAHLSA)</td>
<td>Interview</td>
<td>Based on REALM. 50 words, but includes comprehension test (choosing other words of similar meaning)</td>
<td>3–6 min</td>
<td>Score 0–50</td>
<td>&lt;37: inadequate HL, 38–50: adequate HL</td>
</tr>
<tr>
<td>Test of Functional Health Literacy in Adults (TOFHLA)</td>
<td>Numeracy section interview administered</td>
<td>3 passages of text, uses modified Cloze’s procedure where every 5th–7th word is omitted and respondent selects from four options. Interviewer administered 17-item numeracy component.</td>
<td>Up to 22 min</td>
<td>Literacy 0–50, Numeracy 0–50. Total 0–100</td>
<td>0–59: inadequate HL, 60–74: marginal HL, 75–100: adequate HL</td>
</tr>
<tr>
<td>Short form TOFHLA (STOFHLA)</td>
<td>Numeracy section interview administered</td>
<td>36 reading comprehension items. Sometimes includes 4 numeracy items in addition</td>
<td>Less than 10 min (7 min if using reading comprehension items only)</td>
<td>Total weighted score 0–100</td>
<td>0–53: inadequate HL, 54–66: marginal HL, 67–100: adequate HL</td>
</tr>
<tr>
<td>Newest Vital Sign (NVS)</td>
<td>Interview</td>
<td>6 questions relating to nutrition information from an ice cream container</td>
<td>3 min</td>
<td>0–6</td>
<td>0–1: high likelihood of marginal/inadequate HL, 2–3: possibility of marginal/inadequate HL, 4–6: adequate HL</td>
</tr>
</tbody>
</table>

In observational studies) [35]: setting of sample (e.g. primary or secondary care), definition of nature of sample, sampling method, response rate, validity of HL measure used, main outcome variables, potential for bias, potential for unrecognised confounders (assessed by identifying variables known to be associated with HL in other studies not controlled for in the analyses) and statistical methods (including whether the prevalence estimates were age standardized, the presence of a sample size calculation, the measure of precision of HL prevalence).

Statistical analysis

A prevalence value for limited HL was extracted from each of the studies and 95% confidence intervals (CIs) calculated. Meta-analysis was performed to analyse and summarize the observations using the ‘metan’ command in Stata (version 11), using a random-effects model to allow for between- and within-study heterogeneity, to give an overall prevalence value. The degree of heterogeneity was indicated using the I² statistic (the percentage of total variation in the estimated effects across studies that is due to heterogeneity rather than to chance) [36].

Results

Eighty-two studies were identified from the search strategy. Sixty-eight did not meet inclusion criteria on abstract review, leaving 14 studies, of which 8 were excluded on full-text review, leaving a final inclusion of 6 studies (Figure 1) [30, 37–41]. A summary of the included studies is shown in Table 2. All studies were conducted in the USA, all were in English language. Four studies used the REALM to measure HL, and two studies used STOFHLA (one of which also used an adapted REALM measure specific for transplant patients).

Five were cross-sectional studies and one baseline data from a cohort study.

Five were conducted in dialysis units and one in a nephrology clinic setting. The total number of patients in all studies was 1405 (median study size 206, range 50–480 participants).
Methodological quality of included studies

**Sampling.** None of the studies used a random sampling procedure. One used consecutive sampling, one convenience sampling (attending a nephrology clinic), three used volunteer samples and for one, it was not possible to define the sampling method.

**Non-response or selection bias.** All of the studies were identified as having potential for selection bias. For example, in the cohort study, participants were selected if they were deemed ‘eligible to participate in a patient education programme by local nephrology clinical care staff’ [37]. This is recognized as a potential weakness by the authors. Many of the studies excluded non-English speakers, people with cognitive impairment, people living in nursing homes and people with poor vision. The response rate was available for four of the studies and ranged from 26% [40] to 67% [41], leading to the possibility of non-responder bias in these studies.

**Confounding.** All studies only reported overall prevalence with no age sex standardization.

Residual confounding was considered unlikely to influence the prevalence of limited HL. However, with regard to the associations identified, some studies did not appear to control for potentially important confounding factors such as education status and income (Table 3).

Prevalence of limited HL

Prevalence of limited HL (see Table 1 for definitions of HL levels) varied from 9 to 32% (Lower quartile 16.5%, median 25%, upper quartile 32%, interquartile range 15.5%) and there was significant heterogeneity ($I^2 = 2.9\%$). The pooled prevalence of limited HL in all studies was 22.7% (95% CI 20.6–24.8%) (Figure 2).

**Associations of limited HL**

The associations of limited HL identified in the studies are shown in Table 3.

Four studies identified associations of limited HL with lower educational attainment, and three with lower income. Two studies identified associations of limited HL with male gender, and two with non-white populations. Other associations, including veteran status, non-married status and greater level of comorbidity, were identified in individual studies. There was conflict between two studies over association with catheter versus fistula/graft use for dialysis. The cohort study identified an association of limited HL with increased mortality in ESKD [37].

Discussion

**Principal findings**

Limited HL is common in CKD, with an overall prevalence in all the studies of ~23%. However, the significant heterogeneity between studies, and the paucity of HL research to date in CKD, means that this estimate should be interpreted as indicative of magnitude rather than a precise measure. Independent associations of limited HL in CKD populations common to several studies included lower education attainment and low income, raising the possibility of an important role for limited HL in contributing to socio-economic inequalities. Other important associations of limited HL in individual studies were lower levels of kidney disease knowledge [41], lower likelihood of referral for transplant [40] and higher mortality [33].

We are not aware of any previous review of HL prevalence and its associations in studies of CKD, although a previous narrative review identified many of the key issues in CKD populations [31]. A previous systematic review aiming to identify the prevalence of limited HL in a wide variety of populations (including patients and non-patients) in the USA identified 85 studies and gave a weighted prevalence of 26% but with a very wide range (0–68%) [33]. The reviewers recognized that they could not conclude that this was a nationally representative prevalence estimate. Our study supports this by demonstrating the wide variation in limited HL prevalence between studies of clinical populations. It is possible that limited HL is more common in populations of people with CKD than the general population, due to the increased prevalence of CKD in older populations and populations with a lower socio-economic profile, although this has not been demonstrated conclusively by this review [13].

Strengths and weaknesses

Strengths of this review included a broad search strategy that included multiple databases, clear eligibility criteria, assessment of study quality and multiple search terms for many aspects of HL. However, there were some important
<table>
<thead>
<tr>
<th>Study</th>
<th>Date of publication</th>
<th>Location</th>
<th>Chronic condition</th>
<th>n (with CKD)</th>
<th>Median age (yrs) [mean]</th>
<th>Main aim</th>
<th>Study design</th>
<th>Setting</th>
<th>Participants</th>
<th>Health literacy measure used</th>
<th>Main outcome variables</th>
<th>Prevalence of limited HL (%)</th>
<th>Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cavanaugh 1</td>
<td>2010 USA</td>
<td>USA</td>
<td>CKD (haemodialysis)</td>
<td>480</td>
<td>62</td>
<td>Characterize prevalence and associations of limited HL + risk of all-cause mortality in patients initiating chronic haemodialysis</td>
<td>Cohort</td>
<td>77 dialysis units across US</td>
<td>Adults &gt;18 ‘eligible for patient education programme’</td>
<td>REALM</td>
<td>Health literacy, survival (adjusted HR)</td>
<td>32</td>
<td>Limited HL associated with male, non-white, less education, not married status, lower serum albumin and mortality</td>
</tr>
<tr>
<td>Cavanaugh 2</td>
<td>2010 USA</td>
<td>USA</td>
<td>CKD (haemodialysis)</td>
<td>50</td>
<td>[51]</td>
<td>Association between HL and type of dialysis access used</td>
<td>Cross-sectional</td>
<td>Dialysis unit</td>
<td>Adults on haemodialysis</td>
<td>REALM</td>
<td>Prevalence of limited HL, catheter use for dialysis (rather than AVF or graft)</td>
<td>32</td>
<td>Limited HL associated with male gender and greater likelihood of catheter use</td>
</tr>
<tr>
<td>Gordon</td>
<td>2009 USA</td>
<td>USA</td>
<td>CKD (post-transplant)</td>
<td>124</td>
<td>[47]</td>
<td>Relationship between HL, transplant knowledge and graft function</td>
<td>Cross-sectional</td>
<td>Post-transplant clinic visit</td>
<td>Adults &gt;18 taking immunosuppressants post-kidney transplant</td>
<td>STOFHLA T REALM-T (relevant to transplant)</td>
<td>Association between HL measures and demographic variables and graft function measures</td>
<td>9</td>
<td>Limited HL associated with less education, lower income and non-married status</td>
</tr>
<tr>
<td>Green</td>
<td>2011 USA</td>
<td>USA</td>
<td>CKD (haemodialysis)</td>
<td>288</td>
<td>64</td>
<td>Prevalence and associations of limited HL in haemodialysis patients</td>
<td>Cross-sectional</td>
<td>9 outpatient dialysis units</td>
<td>&gt;17, English speaking, outpatients on dialysis</td>
<td>REALM</td>
<td>HL, association with ethnicity, education, income, veteran status, comorbidity</td>
<td>16</td>
<td>Limited HL associated with African-American race, less education, lower income and veteran status</td>
</tr>
<tr>
<td>Grubbs</td>
<td>2009 USA</td>
<td>USA</td>
<td>CKD (haemodialysis)</td>
<td>62</td>
<td>[52.4]</td>
<td>Association of poor HL with access to kidney transplant</td>
<td>Cross-sectional</td>
<td>5 outpatient dialysis units</td>
<td>21–75 years old, black and white only, maintenance dialysis for at least 9 months, never had renal transplant, excluded cog dysfunction</td>
<td>STOFHLA T REALM-T</td>
<td>HL, referral for transplant evaluation, wait-listed for transplant</td>
<td>32</td>
<td>Limited HL associated with older age, lower income, less education and lower hazard of being referred for transplant evaluation</td>
</tr>
<tr>
<td>Wright</td>
<td>2010 USA</td>
<td>USA</td>
<td>CKD (all stages)</td>
<td>401</td>
<td>58</td>
<td>Awareness and knowledge of CKD in patients seeing nephrologists (developing CKD knowledge survey tool)</td>
<td>Cross-sectional</td>
<td>Nephrology clinic</td>
<td>Adults with all stages of CKD seen at least once in a nephrology clinic in the past</td>
<td>REALM</td>
<td>Awareness of CKD by grade of CKD, literacy</td>
<td>18</td>
<td>Kidney disease knowledge</td>
</tr>
</tbody>
</table>
limitations. First, our search strategy may not have covered all potential studies from education databases, though this is considered unlikely for clinical conditions. Secondly, one study was reported in abstract format only, and we were unable to obtain full reports. Our unpublished literature searching was limited, and we may therefore have missed studies, particularly any reported at conferences with a primary focus on education. This raises the possibility that this review is subject to publication bias, although this is less likely for studies of prevalence for which there is no positive or negative outcome that would influence the likelihood of publication.

Limitations of measures of HL

There is also a need to recognize the limitations of the HL measurement tools themselves. Measurement tools such as the REALM and the short form of the Test of Functional Health Literacy in Adults (STOFHLA) were primarily developed to enable clinicians and other health educators to assess the patient’s ability to understand health advice [28, 42, 43]. They are therefore best considered as general screening tools for clinical contexts that measure an aspect of ‘health-related’ literacy, rather than providing a comprehensive assessment of capacity or acting as scalable measures of HL for epidemiological or intervention studies [44]. The prevalence of limited HL in the studies included in this review varied with the measure of HL used. It may be that the prevalence measured in the studies in this review should therefore be considered as the ‘screen positive’ prevalence using the particular screening tool in question. It may also be important for future research to include the development of more specific tools for the early CKD context as has already been developed for transplant patients [39].

Heterogeneity

The small number of studies in this area reduces generalizability. In addition, all studies identified were from the USA which reduces the generalizability of the findings to other countries, particularly given differences in ethnicity and language variables, the non-comparability of health systems and uncertainty about the validity of HL measures in other countries. Moreover, variations in reporting and other country-specific factors mean that direct comparisons are not possible, and standardizing prevalence in the individual studies would require age-specific prevalence data from other countries. There was a considerable variation in population characteristics (such as age distribution and stage of CKD), study size, study design, setting and study quality, particularly weaknesses of sampling and non-response (Table 2). Non-response and exclusions are likely to underestimate the true prevalence as it is likely that those with limited HL were less likely to be included.

The prevalence data reported in this review are not adjusted for age differences, and it is therefore hard to compare between them, and not possible to derive an overall directly standardized prevalence of limited HL. This would require age-specific prevalence data from individual studies.

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The small number of studies in this area reduces generalizability. In addition, all studies identified were from the USA which reduces the generalizability of the findings to other countries, particularly given differences in ethnicity and language variables, the non-comparability of health systems and uncertainty about the validity of HL measures in other countries. Moreover, variations in reporting and other country-specific factors mean that direct comparisons are not possible, and standardizing prevalence in the individual studies would require age-specific prevalence data from other countries. There was a considerable variation in population characteristics (such as age distribution and stage of CKD), study size, study design, setting and study quality, particularly weaknesses of sampling and non-response (Table 2). Non-response and exclusions are likely to underestimate the true prevalence as it is likely that those with limited HL were less likely to be included.

The prevalence data reported in this review are not adjusted for age differences, and it is therefore hard to compare between them, and not possible to derive an overall directly standardized prevalence of limited HL. This would require age-specific prevalence data from individual studies.
ethnicity distribution between the studies reduce generalizability even within the USA.

Most of the studies were conducted in secondary care with populations that included people on haemodialysis, transplant recipients and only one study in a broader CKD outpatient group.

Further research

There is a need for studies that include populations of people with pre-end-stage CKD, and also for non-US studies. HL is important throughout the whole care pathway in CKD, and information needs vary at different stages of CKD. An inadequate level of HL is potentially modifiable through educational interventions, and other measures that improve self-care, and facilitate access to health care and the appropriate uptake and use of health services. Such measures can empower patients to manage their own condition. Understanding the role of limited HL in adversely affecting the disease process and outcomes in CKD is therefore an important goal for health services in many countries and for future research. While CKD is more common in lower socio-economic groups and certain ethnic minorities [13], more evidence is needed on socio-economic disparities in CKD process and outcome (particularly in pre-ESKD stages of CKD) and consideration of the role of limited HL in adversely influencing self-management and shared decision-making earlier in the CKD disease process [45–47]. There is some evidence that community-based chronic disease self-management education programmes can improve health behaviours and reduce hospital admissions and that providing information for patients in an accessible format may improve clinical outcomes [48–50]. This review supports the need to develop and evaluate such interventions in CKD. One study identified, but not included in this review, had investigated numeracy skills in people with CKD and identified that poor numeracy skills are common [51]. This remains an important and under-explored area in CKD where understanding numerical concepts may be vital to informed decision-making. Uncertainties remain about the measurement of HL, the value of measuring HL in clinical contexts and the appropriate interpretation of the results of the different measures (including decisions to adopt a ‘population’ or ‘at risk’ approach). In the context of demographic transition and growing prevalence of CKD, HL, self-management and shared-decision making are set to become increasingly important. This should include an understanding of CKD-related HL as an asset that can improve capacity for self-care, facilitate navigation of the health system and improve the quality of clinician–patient interactions.

Conclusion

This literature review found that limited HL is common among people with CKD using commonly used HL measures. It identified several studies showing associations between limited HL and socio-economic factors (lower education attainment, lower income), and individual studies showing the association of limited HL with certain process and outcome measures (lower likelihood of referral for transplant, higher morbidity). Despite the weaknesses identified in the design of the included studies, this review suggests that limited HL may represent an important determinant of poor outcomes in CKD, though a better understanding of causal mechanisms and the effectiveness of interventions to address HL is required.

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References


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Low- and high-molecular-weight urinary proteins as predictors of response to rituximab in patients with membranous nephropathy: a prospective study

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Abstract

Background. Selective urinary biomarkers have been considered superior to total proteinuria in predicting response to treatment and outcome in patients with membranous nephropathy (MN).

Methods. We prospectively tested whether urinary (U) excretion of retinol-binding protein (RBP), α1-microglobulin (α1M), albumin, immunoglobulin IgG and IgM and/or anti-phospholipase 2 receptor (PLA2R) levels could predict response to rituximab (RTX) therapy better than standard measures in MN. We also correlated changes in antibodies to PLA2R with these urinary biomarkers.

Results. Twenty patients with MN and proteinuria (P) >5 g/24 h received RTX (375 mg/m2 × 4) and at 12 months, 1 patient was in complete remission (CR), 9 were in partial remission (PR), 5 had a limited response (LR) and 4 were non-responders (NR). At 24 months, CR occurred in 4, PR in 12, LR in 1, NR in 2 and 1 patient relapsed. By simple linear regression analysis, UlgG at baseline (mg/24 h) was a significant predictor of change in proteinuria at 12 months (Δ proteinuria) (P = 0.04). In addition, fractional excretion (FE) of IgG, urinary alpha 1 microglobulin (Uα1M) (mg/24 h) and URBP (μg/24 h) were also predictors of response (P = 0.05, 0.04, and 0.03, respectively). On the other hand, UlgM, FEIgM, albumin and FE albumin did not predict response (P = 0.10, 0.27, 0.22 and 0.20, respectively). However, when results were analyzed in relation to proteinuria at 24 months, none of the U markers that predicted response at 12 m could predict response at 24 m (P = 0.55, 0.42, 0.29 and 0.20). Decline in anti-PLA2R levels was associated with and often preceded urinary biomarker response but positivity at baseline was not a predictor of proteinuria response.

Conclusions. The results suggest that in patients with MN, quantification of low-, medium- and high-molecular-weight urinary proteins may be associated with rate of response to RTX, but do not correlate with longer term outcomes.

Keywords: membranous nephropathy; rituximab; urinary proteins

Introduction

Idiopathic membranous nephropathy (MN) is a common immune-mediated glomerular disease and remains the leading cause of nephrotic syndrome in Caucasian adults