Use of protein:creatinine ratio measurements on random urine samples for prediction of significant proteinuria: a systematic review

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CRD summary
This review assessed the utility of the protein:creatinine ratio in a random urine sample to rule out proteinuria as defined by 24-hour urine protein measurement. The authors' conclusion that the protein:creatinine ratio can be used to rule out proteinuria was somewhat optimistic given the data presented. Limitations in the search strategy and methodology used in the review could also cast doubt upon its findings.

Authors' objectives
To assess the utility of the protein:creatinine ratio in a random urine sample to rule in or rule out proteinuria. The utility of the protein:osmolality ratio was considered as a secondary objective.

Searching
MEDLINE and EMBASE were searched to identify full papers and letters; the search terms were reported. The reference lists of included studies were examined for additional papers.

Study selection
Study designs of evaluations included in the review
No inclusion criteria for the study design were defined.

Specific interventions included in the review
Studies assessing the protein:creatinine or protein:osmolality ratio in random urine samples were eligible for inclusion. The included studies were required to define the ratio cut-off values used to indicate proteinuria, the timing of random urine collections and the analytical methods used. The included studies used a range of protein:creatinine ratio cut-off values (17 to 56.5 mg/mmol).

Reference standard test against which the new test was compared
The included studies were required to use 24-hour urine protein measurement as the reference standard in all participants, with defined cut-off values and analytical methods. The majority of the included studies used 300 mg/day as the cut-off value defining proteinuria.

Participants included in the review
The included studies were required to define their patient population (number, age, pathology, any exclusion criteria used). Ten of the 16 included studies were of pregnant women with pre-eclampsia.

Outcomes assessed in the review
The included studies were required to report sufficient data to calculate diagnostic outcome measures: sensitivity, specificity and likelihood ratios (LRs).

How were decisions on the relevance of primary studies made?
Two authors screened the retrieved papers for inclusion.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The reviewers calculated diagnostic outcome measures from the data presented in the included studies.

**Methods of synthesis**

**How were the studies combined?**

Summary estimates of sensitivity, specificity, positive and negative LRs, and the diagnostic odds ratio were calculated for the 10 studies of protein:creatinine ratio in pregnant women with pre-eclampsia, using a random-effects model. A summary receiver operating characteristic curve was constructed for all 16 studies of the protein:creatinine ratio.

**How were differences between studies investigated?**

Between-study heterogeneity was assessed visually using forest plots and statistically using the chi-squared test. The Moses and Littenberg method was used to assess the threshold effect and the presence of significant between-study heterogeneity not accounted for by variation in threshold.

**Results of the review**

Sixteen studies of protein:creatinine ratio (1,781 participants) were included. Data on the correlation between protein:creatinine ratio and 24-hour urine protein were presented for a further 4 studies (812 participants), and between protein:osmolality ratio and 24-hour urine protein for 2 studies (323 participants).

Protein:creatinine ratio (16 studies).

The sensitivity and specificity values derived from the included studies ranged from 69 to 96% and from 41 to 97%, respectively. The positive and negative LRs ranged from 1.8 to 16.5 and from 0.06 to 0.35, respectively. The data suggested a strong correlation (r) between protein:creatinine ratio and 24-hour urine protein (r between 0.56 and 0.98; p-values between 0.01 and 0.0001).

Protein:creatinine ratio in pregnant women with pre-eclampsia (10 studies).

The pooled estimates were sensitivity 90% (95% confidence interval, CI: 86, 93), specificity 78% (95% CI: 68, 88), positive LR 4.2 (95% CI: 2.6, 6.9) and negative LR 0.14 (95% CI: 0.09, 0.24). There was significant between-study heterogeneity in specificity and positive and negative LRs (p<0.0001, p<0.0001 and p<0.015, respectively).

**Authors' conclusions**

The protein:creatinine ratio on a random urine sample provided evidence to rule out proteinuria as defined by a 24-hour urine protein measurement.

**CRD commentary**

The review addressed a clearly stated research question, which was well defined by its inclusion criteria. A literature search that was limited to two bibliographic databases, as well as the use of search terms relating to diagnostic outcome measures, might have resulted in the omission of some relevant data. Searches were restricted to full studies and letters, leaving open the possibility of publication bias; this was not assessed. The methodological quality of the included studies was not assessed and the reporting of review methodology was limited. It was therefore impossible to assess the potential impact of error or bias, introduced as a result of methodological flaws in the included studies and/or the review itself, upon the findings of the review.

The methods used to pool the included studies were broadly appropriate to the meta-analysis of diagnostic accuracy studies. However, the calculation of pooled estimates of LRs in the presence of significant between-study variation is of limited value. Similarly, the presence of threshold effect (between-study variation due to the use of different cut-offs) was implied, making the pooling of studies across all thresholds of questionable value. The authors concluded that the protein:creatinine ratio is useful for ruling out significant proteinuria. The strength of this conclusion is not supported by the data presented, either for all of the included studies or for the population of pregnant women.
**Implications of the review for practice and research**

**Practice:** The authors stated that the protein:creatinine ratio in a random urine sample might be used to rule out significant proteinuria as defined by 24-hour urine protein measurement. When results above the cut-off value for protein:creatinine ratio are found, a 24-hour urine collection and protein measurement is indicated.

**Research:** Further prospective studies are required to validate these results in specific populations.

**Bibliographic details**


**PubMedID**

16020501

**DOI**

10.1373/clinchem.2005.049742

**Original Paper URL**

http://www.clinchem.org

**Indexing Status**

Subject indexing assigned by NLM

**MeSH**

Creatinine /urine; Humans; Likelihood Functions; Predictive Value of Tests; Proteinuria /diagnosis /urine; Reproducibility of Results; Sensitivity and Specificity; Urinalysis /statistics & numerical data

**AccessionNumber**

12005001332

**Date bibliographic record published**

31/12/2007

**Date abstract record published**

31/12/2007

**Record Status**

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