

# Assessing urinary albumin excretion in pre-eclamptic women: which sample to use?

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**Objective** To evaluate whether the gold standard of 24-hour urine collection for measuring albumin excretion in pre-eclamptic women could be substituted by shorter collection periods.

**Design** Prospective study.

**Setting** Fetal maternity ward, university hospital.

**Participants** Thirty women with pre-eclampsia and a positive urinary test strip for protein of at least 2+.

**Methods** From each woman, within a 25-hour period, three spot, two 12-hour (day and night) and one 24-hour urine sample were collected. Urine albumin concentrations in milligrammes per litre were analysed by rate nephelometry on a Beckman Array protein system. The urinary albumin concentrations in the spot and the 12-hour samples were compared with the concentration in the 24-hour urine collection.

**Main outcome measures** Urinary albumin concentrations in spot and 12-hour samples measured against the standard 24-hour albumin excretion.

**Results** Albumin concentrations in the day and night collection fitted closely with the concentrations of the 24-hour collection. The median difference between the 24-hour and the day collection was  $-3$  mg/L (interquartile range  $-264$  to  $116$  mg/L). The median difference between the 24-hour and the night collection was  $17$  mg/L (interquartile range  $-186$  to  $210$  mg/L). The association of urinary albumin concentration in the 24-hour collection and the spot samples was much weaker. Of the spot urine samples, the albumin concentration in the sample taken on the morning after admission to hospital was closest to the 24-hour urinary albumin excretion, with a median difference of  $-62$  mg/L (interquartile range  $-1131$  to  $285$  mg/L).

**Conclusion** The gold standard of 24-hour urinary excretion for assessment of albuminuria in pre-eclamptic women can be substituted with a 12-hour collection. Spot urine samples were inaccurate and are therefore not recommended for quantification of albumin excretion.

## INTRODUCTION

Albuminuria is an important sign of pre-eclampsia and repeated urine analyses to screen for albuminuria are part of standard antenatal care. These urine analyses are performed on random spot urine specimens using a test strip assay, being a procedure that is acceptable to most pregnant women. However, if a test strip is positive for protein 2+ or more in the absence of bacteriuria, the next step is usually a 24-hour urine collection for quantification of albumin. The 24-hour urine collection is inconvenient for the woman,

costly and may also be inaccurate due to incomplete collection.

When pre-eclampsia with persistent albuminuria develops, urinary albumin excretion is monitored by frequent 24-hour urine samples. The purpose of this tedious surveillance is that increased albumin excretion is a sign of aggravation of pre-eclampsia and reflects serious nephropathy. Massive albumin excretion may result in planned preterm delivery.

Collection of urine for determining albumin excretion has been studied in diabetic patients<sup>1–5</sup>. In the Saint Vincent declaration on diabetic nephropathy<sup>6</sup>, the 24-hour urine collection is recommended as the standard when screening for microalbuminuria. If urine collection is not possible, a morning urine sample can be used, or, as a third option, a semiquantitative test strip. These recommendations are based on the circadian rhythm in urinary albumin excretion<sup>7</sup>. However, for pregnant women, particularly if in hospital, the circadian variation in albumin excretion is smaller or absent<sup>8</sup>, and it may therefore be possible to use shorter collection periods.

The aim of this study was to evaluate whether a 24-hour urine collection for measuring urinary albumin excretion in

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pre-eclamptic women could be substituted by a 12-hour collection or spot urine samples.

## METHODS

Thirty women with pre-eclampsia admitted to the ward at the Department of Obstetrics and Gynaecology, Uppsala University Hospital were included in the study. The criteria for inclusion were a positive urinary test strip for protein (BM-test-GP, Roche Diagnostics, Mannheim, Germany) of at least 2+, corresponding to an albumin concentration of more than 500 mg/L, and a planned 24-hour urine collection for quantitative albumin measurement. Women with upper urinary tract infections, defined as a positive urine culture and fever, were not included. Informed consent was obtained from all women. Women admitted to the antenatal ward due to pre-eclampsia are usually prescribed moderate bed rest, that is, that they are advised to rest but are free to move around in the hospital area. Most women have their meals in the department's dining room where they may also watch television. Bed rest was not formally monitored in the women in this study, but was estimated that during the day most women spent 4 to 5 hours outside their rooms.

There were 23 nulliparae and 7 multiparae. Two women were smokers and 23 were non-smokers. Information on smoking habits was missing for five women. Antihypertensive drugs, primarily labetalol, nifedipine or isradipine, were prescribed to 23 women. Further details are given in Table 1.

From each woman, three spot urine samples, two 12-hour and one 24-hour urine collection, were collected. Urine collection started on the first morning after admission to the hospital and all samples were collected within a period of 25 hours. The procedure is described in Fig. 1. Before the urine collection, all women were carefully instructed on the procedure. The urine specimens were stored at 4°C before analysis. Urine albumin was analysed by rate nephelometry on a Beckman Array protein system (Beckman Instruments, USA), according to the recommendations of the manufacturer. Plasma albumin and uric acid were analysed on a Hitachi 911 (Roche Diagnostics Scandinavia, Sweden). Plasma albumin was analysed by a bromocresol green method.

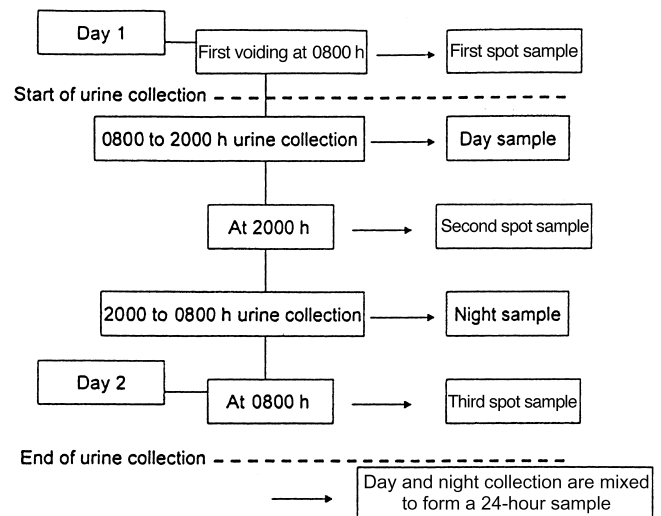


Fig. 1. Flow chart for collection of urinary samples.

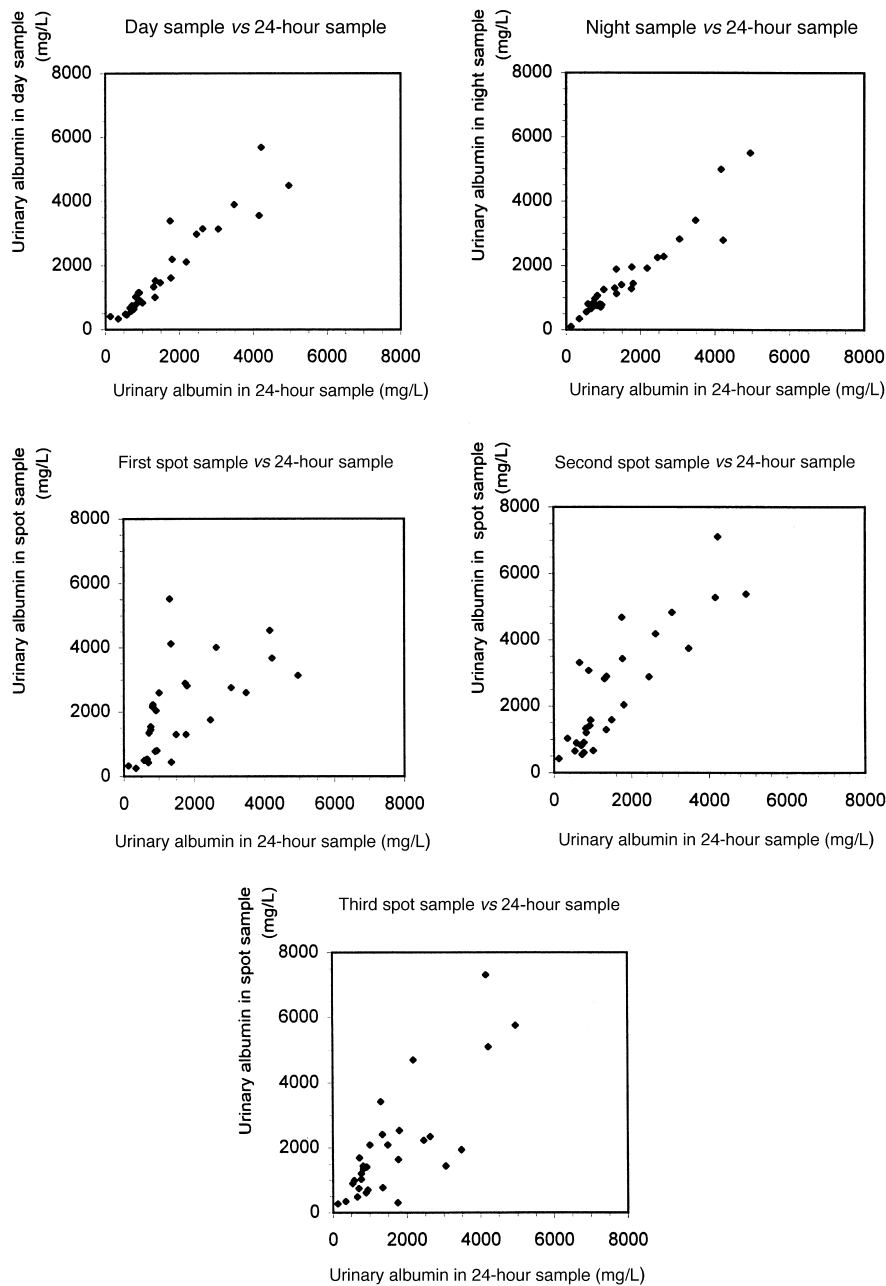
As the albumin excretion in the spot urine samples was reported as concentrations in milligrammes per litre, all values are presented as such. Agreement in albumin excretion between the 24-hour collection and the shorter collection periods is shown graphically in Fig. 2. Differences in albumin excretion are presented as median differences together with interquartile ranges. We considered interquartile range a better estimate than range when describing dispersion in differences. In Fig. 3, median differences and interquartile ranges are shown graphically, together with mean differences and ranges.

## RESULTS

The mean 24-hour urine production was 2.1 L (SD 1.0 L) and the median 2.0 L (range 0.8 to 4.2 L). The mean 24-hour urinary albumin excretion was 3.0 g/L (SD 2.0 g/L) and the median 2.6 g/L (range 0.2 to 9.0 g/L). The mean plasma albumin concentration was 31 g/L (SD 4.3 g/L) (reference interval: 37–48 g/L), and the mean plasma uric acid concentration was 397 µmol/L (SD 71 µmol/L) (reference interval: 120–340 µmol/L). There were 28 complete urine samples. For two of the women, one and two spot

Table 1. Characteristics of the participants.

	Mean	Median	Range
Age (years)	28.9	28	23–39
Gestational age at time of admission to hospital (days)	234	241	170–275
Weight gain during pregnancy (kg)	14.9	15.1	6.6–28.0
Systolic blood pressure in early pregnancy (mmHg)	124	122	85–145
Diastolic blood pressure in early pregnancy (mmHg)	77	80	60–95
Systolic blood pressure at time of admission to hospital (mmHg)	153	151	116–183
Diastolic blood pressure at time of admission to hospital (mmHg)	94	97	76–108



**Fig. 2.** Albumin concentration in 12-hour and spot urine samples in relation to albumin concentration in 24-hour samples. The first and third urine spot samples are morning samples. The second spot sample was collected at 2000 h.

urine samples, respectively, were missing. The albumin concentration in the samples for each of the 30 women is shown in Table 2.

Urine albumin concentrations for the three spot urine samples as well as the two 12-hour samples in relation to the 24-hour sample are shown graphically in Fig. 2. Albumin concentrations in the day and night samples agreed well with concentrations of the 24-hour samples. The median differences between the 24-hour and the day and night albumin concentrations were  $-3$  mg/L (interquartile range  $-264$  to  $116$  mg/L), and  $17$  mg/L

(interquartile range  $-186$  to  $210$  mg/L), respectively (Fig. 3). The median differences in albumin concentration between the 24-hour and the spot samples were higher than those found for the 12-hour samples. The median difference in albumin concentration between the 24-hour and the first spot sample was  $-62$  mg/L (interquartile range  $-1132$  to  $285$  mg/L). The median differences between the 24-hour albumin concentration and the second and third spot samples were  $-434$  mg/L (interquartile range  $-1540$  to  $-141$  mg/L) and  $-395$  mg/L (interquartile range  $-794$  to  $230$  mg/L), respectively. Apart from the night sample,

**Table 2.** Urinary albumin excretion (mg/L) in six different samples in 30 women with pre-eclampsia. All samples were collected within a 25-hour period.

Participant	24-hour sample	Day sample	Night sample	First spot sample	Second spot sample	Third spot sample
1	2629	3150	2289	4010	4180	2340
2	917	1150	707	2040	1420	1410
3	3050	3140	2831	2750	4830	1440
4	1340	1010	1889	4120	1290	2410
5	3479	3900	3420	2590	3740	1930
6	701	585	823	431	818	751
7	662	677	658	537	3310	488
8	895	1159	802	784	3070	616
9	765	698	775	1540	606	1040
10	942	901	783	798	1580	703
11	765	640	970	1450	906	1210
12	537	487	558	missing	656	904
13	2180	2110	1920	missing	missing	4700
14	1350	1520	1129	446	2890	777
15	2460	2980	2250	1750	2880	2230
16	817	1022	757	2160	1330	1440
17	1750	3391	1280	2890	4680	306
18	1484	1460	1406	1300	1590	2090
19	4223	5680	2807	3670	7110	5100
20	345	336	345	257	1030	347
21	720	750	783	1350	551	1690
22	4956	4491	5505	3130	5390	5750
23	1767	1953	1612	1300	3430	1640
24	4164	4997	3559	4540	5280	7310
25	1302	1333	1305	5520	2820	3420
26	1800	2190	1445	2810	2040	2530
27	827	792	1066	2220	1200	1350
28	1003	837	1254	2590	664	2090
29	578	457	807	499	894	1000
30	128	411	98	331	424	275

the albumin excretion was over-estimated in all samples when compared with the 24-hour albumin concentration, as indicated by the negative values for median and mean differences (Fig. 3).

Based on plots of the difference between the 24-hour and the day and night albumin concentrations *vs* the average of the two measurements, we found no evidence that the differences between the 24-hour and the 12-hour samples depended on the magnitude of the measurements<sup>9</sup>.

## DISCUSSION

In this study in women with pre-eclampsia who had significant albuminuria, we found good agreement between urinary albumin concentrations measured in samples collected for 12 hours and the traditional 24-hour collections. We also tested the validity of urinary albumin concentrations measured by the spot urine samples taken at specific times in the morning and in the evening measured against the standard, 24-hour albumin excretion. The differences between the 24-hour collection and the spot samples were too great to be acceptable in clinical practice.

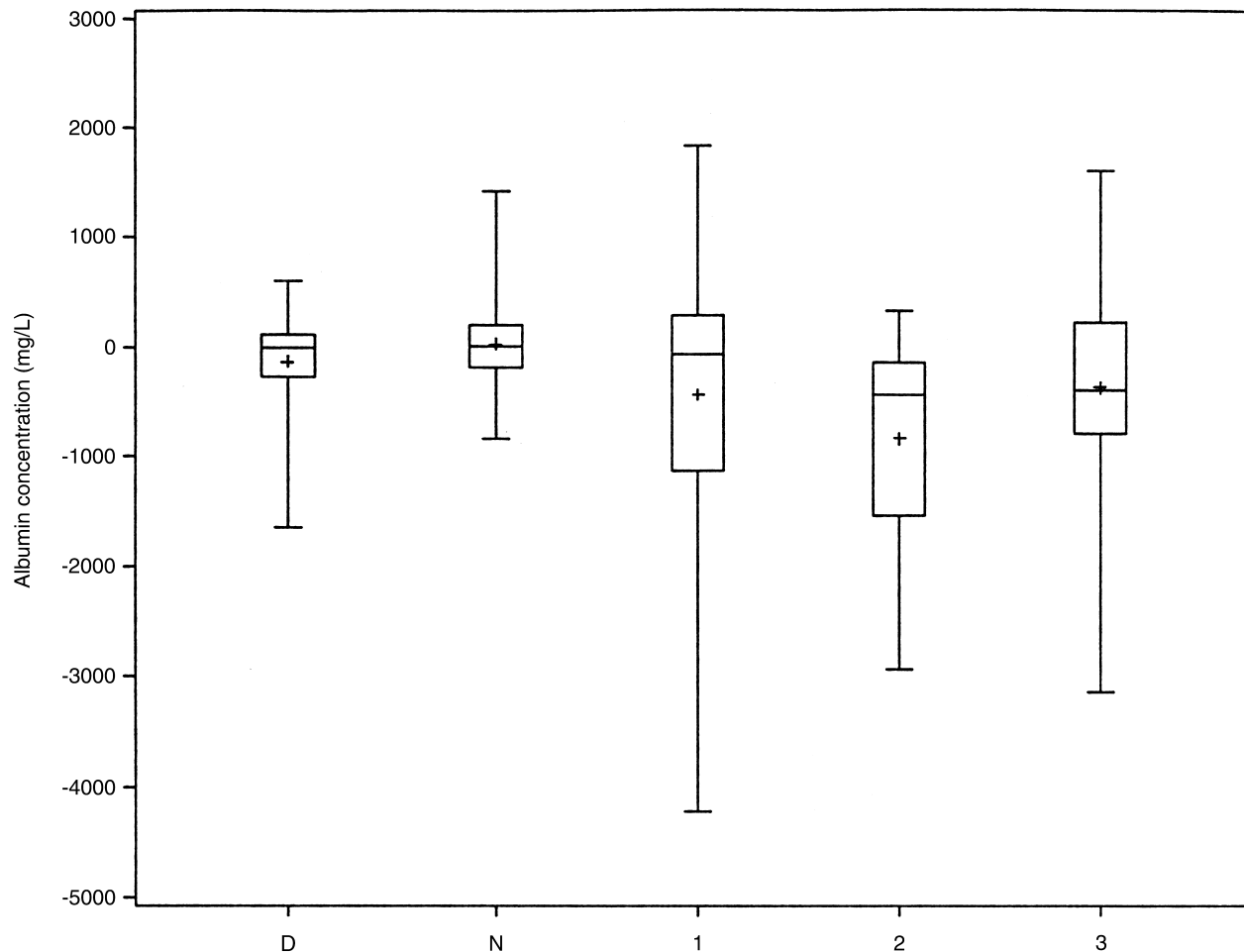
Although the agreement between albumin concentrations in the 24-hour and the 12-hour day sample was slightly better than that of the 12-hour night sample ( $-3$  mg/L *vs*

17 mg/L median differences), the night sample was the only one that did not over-estimate albumin excretion. Over-estimation of albumin excretion may lead to interventions such as planned preterm delivery to be performed earlier than required. Under-estimation of albumin excretion, however, may delay detection of severe nephropathy resulting in damage to the kidneys.

Urinary albumin excretion is, at least in diabetic patients, known to have day-to-day variability<sup>10</sup>; presumably, the same is true in pre-eclampsia. However, there is little likelihood that this biologic variability influenced the results as all the samples were collected within 25 hours.

In some studies<sup>1,10</sup>, the urinary albumin/creatinine ratio is a valid estimate of albumin excretion rate, whereas others<sup>2,11</sup> find that adding analyses of creatinine is of limited use and only increases the costs. As the increase in albumin excretion in severe pre-eclampsia occurs rapidly and suddenly<sup>12</sup>, frequent urine analyses are required. These analyses should be valid and easy to perform, and should be as inexpensive as possible. A night urine sample, starting at 2000 h and ending at 0800 h fulfils these requirements and ought to be more acceptable to the woman than a 24-hour collection. A shorter period should reduce the risk of incomplete collection.

This study was performed on women with pre-eclampsia who were admitted to the hospital and who underwent a



**Fig. 3.** Differences in albumin concentrations between 24-hour collection and the shorter collection periods. Values for mean (+) and median (—) differences as well as range (⊥) and interquartile range (□) are shown. D = Differences between 24-hour and day samples, N = Differences between 24-hour and night samples, 1 = Differences between 24-hour and first spot samples, 2 = Differences between 24-hour and second spot samples, 3 = Differences between 24-hour and third spot samples.

regimen including bed rest. As bed rest can influence albumin excretion, the results may apply only to women undergoing this regimen. However, the major difference between women with pre-eclampsia supervised in the antenatal clinic and the women in this study is the severity of the pre-eclampsia. In our clinical practice, women with pre-eclampsia who stay at home are prescribed the same regimen of bed rest. It is therefore likely that a 12-hour urine albumin excretion is valid not only for women with pre-eclampsia admitted to the ward but also for those supervised at home. Obtaining a complete 24-hour urine collection is difficult, particularly in an outpatient setting, and for the woman at home, a night urine collection is easier to complete than a daytime collection.

Although the methods of collection of urine for measurement of albumin excretion have previously been studied in non-pregnant women and in men, there is disagreement over which urine specimen to use<sup>1,2,4,6</sup>. In this study, we found urine spot samples for albumin analysis to be invalid in pregnant women, even though

albumin excretion is more constant than in non-pregnant individuals<sup>8</sup>. We conclude that urine spot samples from any individual, pregnant or not, are of poor clinical value if precise quantification of albumin excretion is required.

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