Original Article

Correlation between Twenty-Four-Hour Urine Urea Nitrogen and Spot Urine Urea Nitrogen in Patients with Non-Hematologic Malignancy

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Background: Malnutrition is a common problem in patients with cancer, especially in cases of non-hematologic malignancy. Twenty-four-hour urine urea nitrogen [UUN] can be used to assess nitrogen balance, which may indicate nutritional status. However, the procedure can be inconvenient. The use of spot urine samples is proposed as an alternative method of estimating 24-hour UUN.

Objective: To study the correlation between 24-hour UUN and UUN values from spot urine samples in patients with non-hematologic malignancy.

Materials and Methods: Twenty-nine patients with non-hematologic malignancy, who were admitted between January 2016 and March 2017, were enrolled in our study. Spot urine samples were taken from patients' first void in the morning, after lunch, and from the last void on the same day. The correlation between both UUN and urine urea creatinine ratio [UUN/UCr] from spot urine samples and 24-hour UUN was analyzed using determining the Pearson correlation coefficient.

Results: The mean 24-hour UUN of the 29 patients who were enrolled was 4.87 g. The mean UUN of spot urine samples from the morning, afternoon, and the last void were 394, 342, and 389 mg/dl, respectively. There were significant correlations between 24-hour UUN and UUN from spot urine samples taken from all time frames ($p<0.001$ for the morning sample, $p = 0.001$ for the afternoon sample, $p = 0.01$ for the last void sample). Additionally, correlation between 24-hour UUN and UUN/Cr from morning spot urine was also significant ($p = 0.02$).

Conclusion: The UUN from spot urine samples were significantly correlated with 24-hour UUN. Therefore, UUN from spot urine, particularly samples taken from the first void, may be used as a nutritional assessment tool, indicating protein metabolism, in patients with non-hematologic malignancy.

Keywords: Urine urea nitrogen, Urine urea to creatinine ratio, Spot urine sample, Cancer, Malnutrition

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Malnutrition is a common problem among patients with cancer, particularly in cases of non-hematologic malignancy. It can lead to higher morbidity, poorer response to anticancer therapy, and increased mortality[1]. Appropriate nutrition therapy, via enteral nutrition and/or parenteral nutrition, could improve nutritional status and clinical outcomes. Nutrition assessment, the first step of the nutrition care process, requires a comprehensive evaluation of a patient history, a physical examination, and laboratory investigations. Nitrogen balance is a key tool for indicating the relationship between the overall nitrogen intake and loss[2-5]. Malnourished patients have a negative nitrogen balance due to inadequate intake to cover losses. Several studies have shown that nitrogen balance measurement can be used to determine the

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nutritional status of cancer patients, which can enable appropriate nutrition management to improve clinical outcomes[6,7]. Since the estimation of nitrogen loss requires measurement of 24-hour urine urea nitrogen [UUN], the procedure may be complicated, inconvenient, and inadequate. Assessment from a spot urine sample may be more feasible for clinical practice. The use of urine urea nitrogen per urine creatinine [UUN/UCr] ratio from a spot urine specimen has been proposed[8-10]. Powel et al, for example, found that UUN and UUN/UCr ratio from random urine samples were able to accurately estimate the dietary protein intake in healthy young men[8]. However, evidence of this method's application is limited in certain population. Therefore, this study aimed to verify the correlation between 24-hour UUN and UUN parameters from spot urine samples in cancer patients.

Materials and Methods

Participants and setting

This was a cross-sectional study. The sample consisted of 29 patients over 18 years old with non-hematologic malignancy who were admitted to Srinagarind hospital from January 2016 to March 2017. The exclusion criteria were acute renal failure, estimated glomerular filtration rate less than 30 ml/min/1.73 m^2 as calculated using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation, liver enzymes more than five times the upper normal limit, shock, sepsis, or having received chemotherapy or radiotherapy within the past two weeks. All enrolled patients received comprehensive information about the study and provided written informed consent.

Sample size

Sample size calculations were based on the primary objective of the study, which was to evaluate the correlation between 24-hour UUN and spot UUN/UCr ratio. A sample size of 29 participants was found to be adequate at a power of 0.8.

Data collection

Baseline data were collected including age, sex, body weight, height, type and stage of cancer, cancer cell type, duration of disease, comorbidity, and current medications. Creatinine height index, which is calculated by comparing the percentage of 24-hour urine creatinine to that of expected 24-hour urine creatinine for height, was used to evaluate nutrition status[10]. Twenty-four-hour urine collection began after the first void of the day (around six am) until the completion of the 24-hour period. Spot urine samples (10 ml) were obtained three times throughout the day. The morning spot urine sample was taken from the first void in the morning, the afternoon spot urine sample was the void between lunch and dinner (12 pm to 5 pm), and the last spot urine sample of the day was obtained before bedtime. All urine specimens were collected in plastic containers at room temperature. The 24-hour urine sample and spot urine specimens were collected on the same day and sent to the central laboratory of Srinagarind hospital for quantitative determination of urea nitrogen and creatinine, which was measured using Roche/Hitachi Cobas C systems (Roche Diagnostic, Indianapolis, USA).

Statistical analysis

Baseline characteristics were analyzed using descriptive statistics. Continuous data with normal distribution was presented as mean and standard deviation. Categorical data was presented as number and percentage. Correlations between 24-hour UUN and UUN/UCr ratio from spot urine samples were presented as Pearson correlation coefficient. All of the data analysis was performed using STATA version 10.1 (StataCorp, College Station, TX, USA).

Ethics approval was provided by the Khon Kaen University Faculty of Medicine ethics committee as instituted by the Helsinki Declaration.

Results

Twenty-nine patients were enrolled in this study. Baseline characteristics are shown in Table 1. The majority of participants were male. The mean age was 54 years old. Gastrointestinal malignancy was the most common cancer in this study. Eighty percent of patients were in advanced stages of the disease (i.e., stage 3 or stage 4). According to creatinine height index, most of the patients were malnourished. All patients were receiving an oral diet and/or enteral nutrition.

The average 24-hour UUN and UCr were 4.87 and 0.8 g/day, respectively (Table 2). The average UUN and UCr of spot samples did not differ significantly by collection time frame. Twenty-four-hour UUN was significantly correlated with UUN/UCr ratio from morning spot urine, with a correlation coefficient of 0.18, but not correlated with that from the afternoon or the last spot urine sample (Table 3). However, 24-hour UUN was significantly correlated with UUN from spot urine samples taken at all time frames. Figure 1 shows a scatter plot of 24-hour UUN and UUN from morning spot urine samples, which demonstrated the strongest

Table 1. Baseline characteristics of the studied population

Characteristics	n = 29 (100%)
Age; years (mean ± SD)	54±14
Sex (%)	
Male	19 (65.5)
Female	10 (34.5)
Weight; kg (mean ± SD)	54.6±12.4
Height; cm (mean ± SD)	161.3±8.6
BMI; kg/m^2 (mean ± SD)	20.9±3.6
GFR; ml/min/1.73 m^2 (mean ± SD)	91.3±22.6
Cancer type (%)	
Central nervous system	1 (3.4)
Head and neck	3 (10.3)
Respiratory	2 (6.9)
Gastrointestinal	17 (58.6)
Bone and soft tissue	6 (20.7)
Cell type (%)	
Adenocarcinoma	12 (41.4)
Squamous	3 (10.3)
Others	2 (6.9)
N/A	11 (37.9)
Cancer stage (%)	
Stage 1	1 (3.4)
Stage 2	3 (10.3)
Stage 3	8 (27.6)
Stage 4	17 (58.6)
Underlying disease (%)	
Type 2 diabetic mellitus	1 (3.4)
Hypertension	1 (3.4)
Chronic kidney disease	1 (3.4)
Duration of cancer diagnosis (%)	
Less than 1 year	22 (75.9)
More than 1 year	7 (24.1)
Current medication (%)	
Steroid	1 (3.4)
Immunosuppressive agents	1 (3.4)
Nutrition status evaluated by creatinine height index	
Normal	1 (3.4)
Mild malnutrition	5 (17.2)
Moderate malnutrition	14 (48.3)
Severe malnutrition	9 (31.0)
Nutrition therapy (%)	
Parenteral	0 (0)
Oral or enteral	29 (100)

SD = standard deviation, N/A = not available

correlation among the three time frames for spot urine sample collection. Additionally, there was a significant correlation between 24-hour UUN/UCr ratio and spot UUN/UCr ratio from the morning sample and, to a lesser extent, the last voided sample. However, although the afternoon sample tended to be correlated to 24-hour UUN/UCr, this correlation was not statistically significant.

Discussion

Most cancer patients are malnourished, a condition that is associated with poor response to anticancer treatment, unfavorable prognosis, and low quality of life. Malnutrition in patients with cancer may be caused by either inadequate nutritional intake or inflammation-induced catabolism[1]. This study found that patients had an average 24-hour UUN of 4.87 g/day, which indicated that they might have low levels of physical stress[11]. Additionally, nutrition status, as evaluated by creatinine height index, indicated that the majority of patients were moderately or severely malnourished. Therefore, the main mechanism of malnutrition in this cohort of cancer patients was inadequate food intake rather than catabolic state. This finding also confirmed the usefulness of UUN as an indicator of protein intake[8,9].

Due to the inconvenience of 24-hour sample collection, a number of researchers have examined whether UUN from a shorter collection duration could be used instead. Widdowson et al. used random urine specimens from African and British children in order to compare their dietary intake[12]. A study by Record et al indicated that there was a strong correlation between six-hour UUN and 24-hour UUN in surgical patients[13]. In addition, Quandt et al proved the accuracy of two-hour UUN determinations in critically ill patients[14]. Sorkness illustrated that 12-hour urine collection could predict 24-hour UUN excretion with an error of less than 10% in patients with trauma[15]. Similarly, a study by Lopez et al found that six-hour urine collection was a feasible alternative for calculating nitrogen balance in infants when taking a 24-hour urine sample was not possible[16]. Candio et al demonstrated that 12-hour urine collection, but not four-hour or eight-hour determinations, provided a satisfactory estimation of 24-hour nitrogen excretion in critically ill adults who were receiving parenteral nutrition[17]. Graves et al showed that both six-hour and 12-hour urine samples may be used to estimate 24-hour nitrogen losses in adult patients with critical illness[18]. However, Ford et al observed hourly variations in urinary nitrogen loss, which limited the use of abbreviated urine sample determination[19]. The present study revealed the usefulness of spot urine collection in cancer patients, showing a significant correlation between UUN from 24-hour samples and all spot urine specimens.

Table 2. Mean and standard deviation of urea and creatinine values from urine specimens

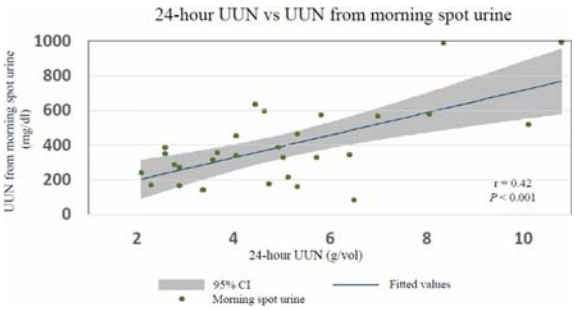
	24-hour urine	Morning spot urine	Afternoon spot urine	Last spot urine
UUN: mean (SD)	4,872 mg (2,288)	394 mg/dl (223)	342 mg/dl (241)	389 mg/dl (256)
UCr: mean (SD)	800 mg (292)	72 mg/dl (40)	65 mg/dl (63)	66 mg/dl (52)
UUN/UCr: mean (SD)	6.14 (1.68)	5.72 (1.81)	5.96 (1.86)	6.30 (1.92)

UUN = urine urea nitrogen; UCr = urine creatinine; UUN/UCr = urine urea nitrogen to urine creatinine ratio; SD = standard deviation

Table 3. Correlation between urea nitrogen obtain from 24-hour urine collection and spot urine samples

	Morning spot urine	Afternoon spot urine	Last spot urine
Correlation between 24-hour UUN and UUN from spot urine samples: pearson correlation coefficient (*p*-value)	0.42 ($p<0.001$)	0.25 ($p = 0.001$)	0.20 ($p = 0.01$)
Correlation between 24-hour UUN and UUN/UCr from spot urine samples: pearson correlation coefficient (*p*-value)	0.18 ($p = 0.02$)	0.0004 ($p = 0.92$)	0.024 ($p = 0.42$)
Correlation between 24-hour UUN/UCr and UUN/UCr from spot urine samples: pearson correlation coefficient (*p*-value)	0.41 ($p<0.001$)	0.09 ($p = 0.09$)	0.56 ($p<0.001$)

UUN = urine urea nitrogen; UUN/UCr = urine urea nitrogen to urine creatinine ratio



UUN = urine urea nitrogen; 95% CI = 95% confidential interval

Figure 1. Scatter plot between 24-hour urine urea nitrogen and urea obtained from the morning spot urine sample.

Additionally, our study established that the strongest correlation was between 24-hr UUN and the UUN from morning spot urine. This finding is supported by the fact that the morning first void may represent the metabolism throughout the preceding night, making it comparable to six-hour or eight-hour urine collection in some previous studies[13,16,18].

Use of the normalized ratio of urinary biomarkers for creatinine is intended to control for variations in urine flow rate with the assumption of constant urine urea excretion[20]. Middendorf et al demonstrated a significant correlation between the UUN/UCr ratio of a spot urine specimen obtained five hours after the last meal of the day and that of the previous 24-hour period[21]. The present study also found a significant correlation between UUN/UCr ratio of 24-hour urine determination and that of spot urine taken in the morning and the last void, but not the afternoon sample. The finding may be explained by variations in urine creatinine excretion, which could occur when urinary biomarker and creatinine generation rates are different[20,22]. Our data showed that the standard deviation of UCr was rather wide in spot urine taken at each time point, particularly during the afternoon. Moreover, the correlations weakened when 24-hour UUN was compared to the UUN/Cr ratio from spot urine samples. Only the UUN/UCr ratio from the morning sample was significantly correlated with 24-hour UUN. Therefore, the UUN/UCr ratio should be interpreted with caution.

Some previous studies have illustrated diurnal variation of urinary urea excretion. Steffee et al, for example, found that there was a rise in UUN during the daylight hours with a nadir during the early morning in healthy adults[23]. A study conducted by Powel et al also demonstrated this finding[8]. This phenomenon might be explained by the effect of dietary intake during

the daytime. However, Sorkness revealed that UUN excretion in the afternoon exhibited negative deviation compared with the other collection periods, despite the patients receiving continuous parenteral nutrition[15]. The authors believed that this was due to diurnal variation in urea excretion. Our study also found slight negative deviation of UUN from the afternoon sample, but this difference was not statistically significant.

One strength of the present study was that all urine samples were handled properly, as they were collected from the hospitalized patients. In addition, this meant that there were no missing nor incomplete samples. However, there were a few limitations: 1) the study did not measure body composition (i.e., fat-free mass), which might affect urea excretion; 2) the correlation coefficient may not be as high as those found in previous studies, which implied there may be additional factors that influenced UUN; 3) the data was not designed to obtain the cut-off value for high or low UUN from the spot urine samples. Further research is needed to prove and to maximize the benefits of spot urine samples.

Conclusion

UUN from spot urine samples, especially those taken in the morning, could be used as an indicator in nutritional assessment comparable to 24-hour UUN in cancer patients. However, this data should be interpreted cautiously.

What is already known on this topic?

We can use 24-hour UUN in determining protein metabolism. UUN may be alternative methods in certain population.

What this study adds?

This study showed the UUN from spot urine samples was correlated with 24-hour in cancer patients. The finding may improve convenience in the process of nutritional assessment.

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Potential conflicts of interest

The authors declare no conflict of interest.

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