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# Eficacia de la medición de nitrógeno ureico urinario para evaluar la adherencia a dietas restringidas en proteínas

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# Efficacy of urine urea nitrogen measurement to assess the compliance with protein restricted diets

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*Authorship declaration: Victoria Pérez, Daniel Bunout and Gladys Barrera designed the project, recruited and followed the participants and analyzed data. Sandra Hirsch and Eduardo Lorca analyzed data and contributed to write the manuscript. All authors are in agreement with the manuscript and declare that the content has not been published elsewhere.*



## RESUMEN

**Introducción:** la restricción proteica es fundamental en el manejo de la enfermedad renal crónica.
**Objetivo:** evaluamos la utilidad de la medición de nitrógeno ureico urinario como marcador de restricción proteica.
**Métodos:** participantes jóvenes sanos fueron divididos aleatoriamente en dos grupos. Un grupo recibió una dieta con 30 kcal/día/kg peso

corporal y 1 g/proteína/día/kg peso corporal y el otro recibió una dieta con la misma cantidad de calorías pero con 0,6 g/kg peso corporal de proteína. Al inicio, a los siete y a los 14 días, los participantes respondieron una encuesta dietaria de recordatorio de 24 horas. Además, recolectaron orina de 24 horas y se les tomó una muestra aislada de orina al comienzo y a los 14 días de la intervención para medir creatinina y nitrógeno ureico.

**Resultados:** cuarenta y un participantes de 29 ± 5 años completaron el estudio. El grupo que consumió 0,6 g/kg de proteínas redujo su ingesta proteica de 0,88 ± 0,06 a 0,59 ± 0,05 g/kg/día durante la intervención. En este grupo se observó una reducción significativa en la excreción urinaria de nitrógeno ureico en 24 horas. No se observó tal reducción en el grupo que consumió 1 g/kg de proteínas. La tasa de probabilidad de detectar una reducción en la ingesta proteica en las encuestas dietarias, cuando se observaba una disminución en la excreción urinaria de nitrógeno ureico/mg creatinina de 24 horas, fue de 5,75 (intervalos de confianza de 95% = 1,29-25,55, p = 0,02). No hubo cambios significativos en la excreción de nitrógeno ureico en las muestras aisladas de orina.

**Conclusión:** las mediciones repetidas de nitrógeno ureico urinario en 24 horas son un marcador de restricción dietaria de proteínas.

**Palabras clave:** Restricción proteica. Nitrógeno ureico. Enfermedad renal.

**ABSTRACT**

**Background:** protein restriction is the mainstay of dietary management of chronic kidney disease.

**Aim:** to assess the usefulness of urine urea nitrogen measurement as a marker of protein restriction.

**Methods:** healthy young participants were randomly divided in two groups. During 14 days, one group received a diet containing 30 kcal/kg body weight and 1 g protein/kg body weight and the other group received a diet with the same amount of calories and 0.6 g/kg of proteins. At baseline, seven days and 14 days, 24 h dietary recalls were answered by the participants. They collected 24 hour urine and provided spot urine samples at baseline and at the end of the intervention, to measure creatinine and urea nitrogen.

**Results:** forty-one participants aged 29 ± 5 years completed the follow-up. According to 24h dietary recalls, the group receiving 0.6 g/kg protein reduced significantly the protein intake during the intervention from 0.88 ± 0.06 to 0.59 ± 0.05 g/kg/day. A significant reduction in 24 h urea nitrogen excretion was also observed in this group. In the group receiving 1 g/kg of protein, no significant changes in 24 h urea nitrogen excretion were observed. Among all participants, the odds ratio of observing a reduction in protein intake in the dietary survey was 5.75 (95% confidence intervals 1.29-25.55, p = 0.02), when a reduction in 24 h urea nitrogen excretion corrected by creatinine was observed. No changes were observed in urea nitrogen excretion in spot urine samples.

**Conclusions:** repeated urea nitrogen excretion measured in 24 h urine samples can be a reliable indicator of dietary protein restriction.

**Key words:** Protein restriction. Urine nitrogen. Kidney disease.



## INTRODUCTION

Most guidelines recommend a dietary protein restriction for patients with chronic kidney disease, aiming at delaying the entry to dialysis and eventually retarding the disease progression. The usual recommendation is to reduce protein intake to 0.6 to 0.8 g/kg/day (1). Another alternative is to reduce protein intake to 0.2-03 g/kg/day and provide keotacid supplements (2).

The problem with protein restriction in ambulatory and usually asymptomatic patients is the compliance with the recommendation and the assessment of such compliance. In general, adherence to dietary changes is complicated to achieve and difficult to monitor. The usual method to determine adherence is the use of dietary recalls but again, these relay on the accuracy and veracity of patients' reports. Thus, this method may become an unreliable source of information if not performed following strict protocols (3).

Urine urea nitrogen excretion has been suggested as other method to assess the adherence to protein restricted diets. Organisms adapt to low protein diets reducing the urine excretion of nitrogen (4). Therefore, the aim of this study was to assess changes in 24 h or spot urine urea nitrogen excretion in healthy individuals consuming a diet providing 1 or 0.6 g/kg/day of proteins in a 14-day period.

**METHODS**

Healthy adults aged between 18 and 45 years, with an estimated glomerular filtration rate over 90 ml/min/1.73 $m^2$, with a body mass index between 19 and 34 $kg/m^2$, not engaged in vigorous physical activities and not taking medications, were invited to participate in the study. The study was approved by the Institute of Nutrition and Food Technology (INTA) Ethics Committee and all participants signed a written informed consent.

At baseline, a 24 h dietary recall was carried out using an atlas of different portions of usual Chilean foods, to increase the accuracy of the recall. Weight and height were measured and participants were requested to collect their urine in a container during 24 h. At the next morning, when they brought their urine collection, a spot urine sample was also obtained.

Subsequently, participants were randomly allocated, using a special iterative software based on random number generation, matching by age and body mass index to two groups receiving diets containing 30 kcal/k and 1 or 0.6 g/protein/day. In the group receiving 0.6 g/kg/day, missing protein calories were substituted by carbohydrates to provide the same amount of calories and micronutrients in both groups. Diet prescription was complemented with pictures of the common portions for Chilean food. One week after the initial assessment, participants were appointed to assess the compliance with the diet and reinforce the prescription when deviations from the initial indication were detected. At the end of the second intervention week, participants provided a new 24 h urine collection and a spot urine sample. A new 24 h dietary recall was done to determine the compliance with the prescribed diet.

In the urine samples, creatinine was determined by the Jaffe kinetic method and urea nitrogen by an UV-kinetic method in a certified clinical laboratory. Urea nitrogen concentration was expressed as absolute values or per mmol of creatinine.

Normality of variable distribution was assessed using Shapiro-Wilks test. Variables with a normal distribution are expressed as mean ± standard deviation, otherwise as median (interquartile range). Differences between values with a normal distribution were assessed using Student's t test. Otherwise, Kruskal-Wallis test was used. Wilcoxon signed-rank test was used to compare changes in urea nitrogen excretion in each group. Correlations between urea nitrogen in spot and 24 h urine samples were determined by Pearson's correlation coefficient. The association between the reduction in protein intake according to the dietary recall and urea nitrogen excretion (corrected or not by creatinine excretion) was analyzed using logistic regression models, using gender and age of participants as covariates.

## RESULTS

Participant flow is shown in figure 1. Fifty five participants were randomized and 14 withdrew from the study. Therefore, 41 completed the two weeks of intervention. Demographic and clinical features of participants who finished the intervention period are shown in table I. Although randomization was carried out balancing for age, participants in the low protein diet who finished the study were significantly younger than their counterparts with normal diet.

According to the dietary recall, protein intake at baseline among participants in the normal and low protein diets was 0.97 ± 0.09 and 0.88 ± 0.06 g/kg/day, respectively (p = NS). A the end of the intervention, the figures were 0.78 ± 0.07 and 0.59 ± 0.05 g/kg/day in the group with normal or low protein intake, respectively (p = 0.02). The changes in 24 h urine urea nitrogen expressed as absolute values or corrected by creatinine excretion are shown in figure 2. There was a significant decrease in absolute urine urea nitrogen excretion among participants in the low protein diet and no changes in their counterparts with normal protein intake. No significant differences between groups were observed when urea nitrogen was corrected by creatinine excretion. When spot urine samples were used, no significant change was observed either. There was no correlation between urea nitrogen measured in spot urine samples and that measured in 24 h samples (r = 0.11 and 0.2 at baseline and the end of the intervention, respectively, p = NS).

On a secondary analysis of all participants, a logistic regression showed that the odds ratio of observing a reduction in protein intake in the dietary survey in all the participants was 5.75 (95% confidence intervals 1.29-25.55, p = 0.02), when a reduction in 24 h urea nitrogen excretion, corrected by creatinine, was observed. The odds ratio for 24 urea nitrogen excretion, not corrected by creatinine, was not significant (2.29, 95% confidence intervals 0.54-9.63, p = 0.26).

## DISCUSSION

We observed that 24 h urea nitrogen excretion significantly decreased after 14 days with a protein restricted diet in participants with normal kidney function. A reduction in 24 h urea nitrogen excretion, corrected by creatinine, indicated that there was a high probability that a reduction in protein intake really occurred. When spot urine samples were used, no significant change was observed.

It is common knowledge that urine nitrogen excretion decreases when dietary protein intake is restricted (5). The time to obtain a stable urea nitrogen excretion after providing a protein restricted diet is approximately eight days (6), therefore the intervention period of 14 days should be more than enough to detect changes in urine urea nitrogen. There is scarce information if this reduction can be detected with mild restrictions, such as those used in chronic kidney disease. Also, working with ambulatory subjects in whom the completeness of urine collections cannot be ascertained is another source of uncertainty about the value of urine urea nitrogen measurements. This study provides evidence to show that, even considering all the possible biases, a reduction in 24 h urea nitrogen excretion can be a reliable indicator of a reduction in protein intake. Moreover, when a reduction in urine urea nitrogen excretion corrected by creatinine is detected, there is a high probability that a reduction in protein intake really occurred.

We also showed that spot urine samples are not reliable for assessing protein intake. Although more feasible than collecting 24 h urine, the variability of urea nitrogen excretion during the day induced by food intake precludes the use of spot samples (7,8). Studies done in hospitalized patients receiving continuous feeding conclude that shorter urine collection times can be used to determine 24 h nitrogen excretion (9). Our results are in contrast with a recent report showing that spot urine samples can accurately predict protein intake in patients with chronic kidney disease. However, this was a cross-sectional study (10). Another study, in which postmenopausal women were supplemented with 45 g of whey protein, showed that urinary urea nitrogen excretion increases with higher protein intake. The authors even calculated a regression equation to predict protein intake from urea excretion. However, this extrapolation is far-fetched considering that the $R^2$ of the equation was only 0.34 (11).

The weaknesses of this study are the unfortunate age imbalance between groups, although this difference should not influence our results. Also, these participants had normal renal function but we considered unethical to have a control group with kidney failure, since the benefits of protein restriction are well known (12). An observational study would be worthwhile among these patients.

In conclusion, a reduction in 24 urine urea nitrogen can be a reliable indicator that subjects are adhering to a protein restricted diet.

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**Table I. Demographic and clinical features of participants who completed the intervention period (expressed as x ± standard deviation)**

| | Group with protein restricted diet (n = 21) | Group with normal protein diet (n = 20) | p |
|---|---|---|---|
| Age (years) | 27.2 ± 4.7 | 31.1 ± 4.8 | 0.01 |
| Body mass index (kg/m$^2$) | 25.9 ± 4.8 | 26.7 ± 3.6 | 0.6 |
| Systolic blood pressure (mmHg) | 117.8 ± 7.7 | 121.5 ± 10.7 | 0.4 |
| Diastolic blood pressure (mmHg) | 74.0 ± 6.8 | 76.7 ± 10.5 | 0.5 |
| Serum creatinine (µmol/l) | 70.5 ± 14.8 | 73.4 ± 11.3 | 0.5 |

**Figure 1**

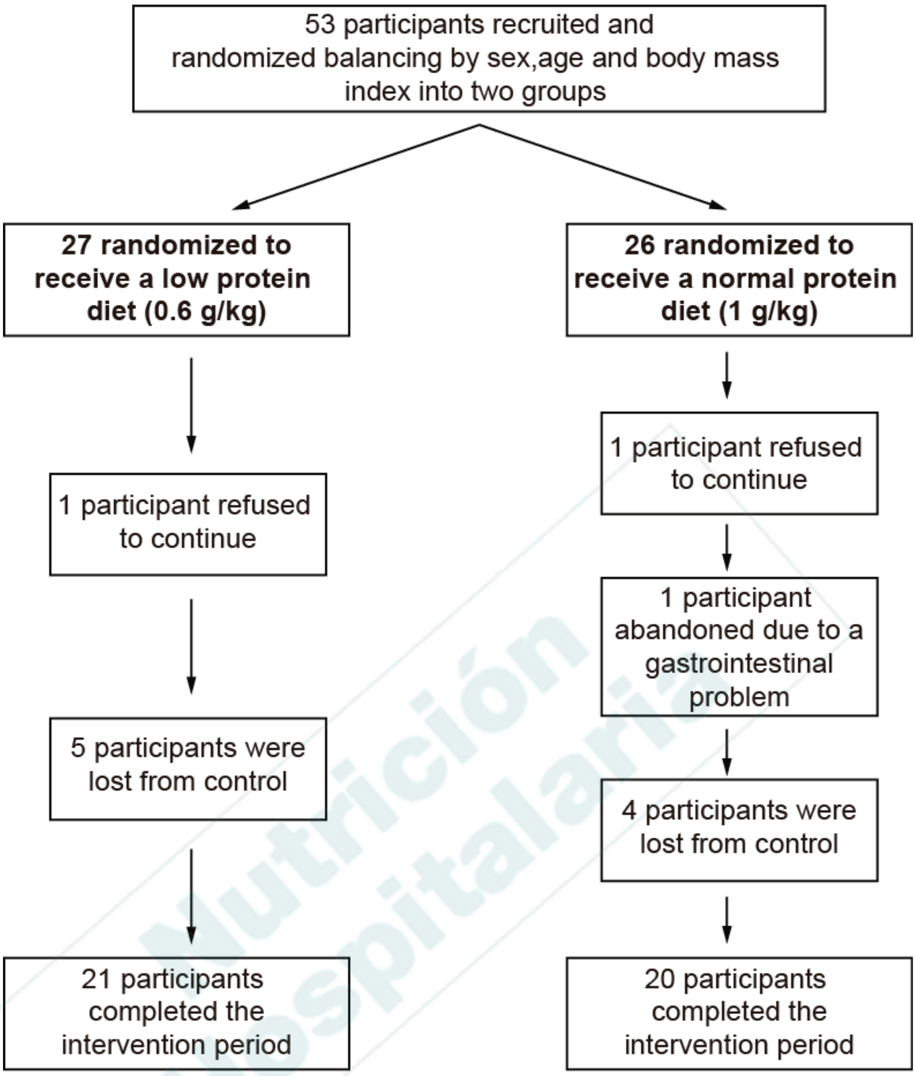
53 participants recruited and randomized balancing by sex,age and body mass index into two groups
27 randomized to receive a low protein diet (0.6 g/kg)
26 randomized to receive a normal protein diet (1 g/kg)
1 participant refused to continue
1 participant refused to continue
1 participant abandoned due to a gastrointestinal problem
5 participants were lost from control
4 participants were lost from control
21 participants completed the intervention period
20 participants completed the intervention period

Fig. 1. Participant flow during the study. Recruited, randomized and lost participants are depicted.

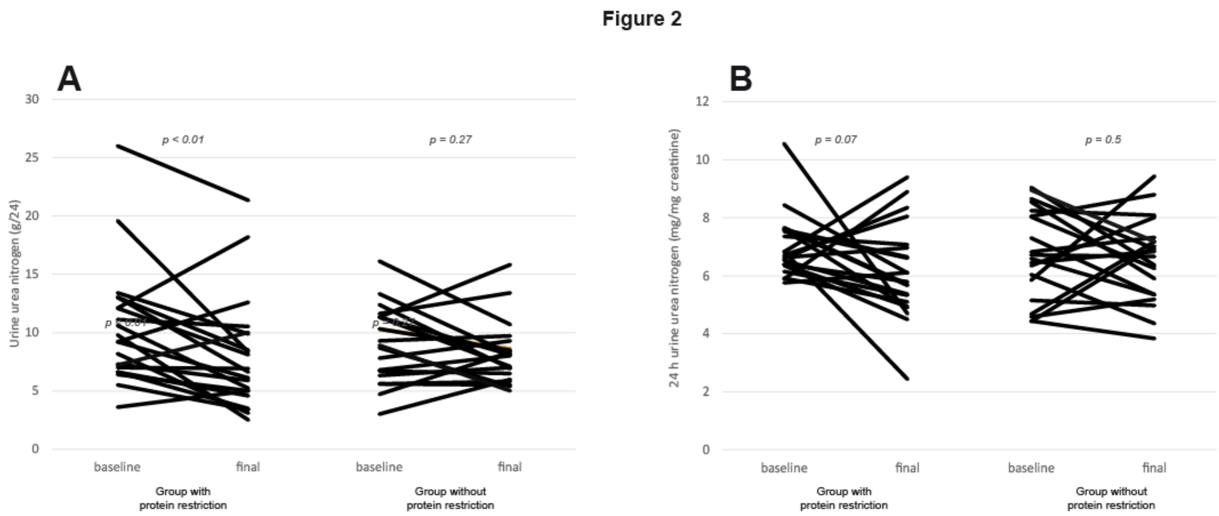


Fig. 2. Changes in 24 h urea nitrogen excretion after the dietary intervention in participants with and without dietary protein restriction. A. Urine urea nitrogen excretion at baseline and at the end of the intervention, expressed as g/24 h. B. Expressed as mg/mg creatinine. Significance of changes from baseline to the end of the intervention was calculated using Wilcoxon signed-rank test.