

Original article

Alpha-1-microglobulin in first morning urine. Clinical interest

Alfa-1-microglobulina en primera orina de la mañana. Interés clínico

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ABSTRACT

Introduction: The reference sample for quantifying alpha-1-microglobulin is 24-h urine. However, although it is usually quantified in the second urine sample of the morning, the first urine sample of the morning is the least influenced by the glomerular filtration rate. Likewise, there are conflicting opinions on the influence of age and gender on quantification.

Patients and methods: A total of 434 urine tests were selected, 182 with a glomerular filtration rate between 4 and 89 mL/min/1.73 m² and 252 with a glomerular filtration rate >90 mL/min/1.73 m². Of these 252, 122 corresponded to first-morning urine samples with a density > 1015 and 130 to 24-h urine samples with a urine volume between 400–3000 mL/24 h, without microalbuminuria. Of the 122, 30 had an alpha-1-microglobulin value > 4.3 mg/L and corresponded to patients with diseases that cause tubular damage. The correlation between first morning and 24-h alpha-1-microglobulin was performed with 42 urine samples, out of the 434 selected, for which both urine samples had been requested.

Results: The correlation between the first morning urine and 24-h urine measurements was 0.92. No statistically significant differences were found between creatinine-corrected alpha-1-microglobulin with age, or between men and women in the first morning urine or 24-h urine samples ($p > 0.05$). The upper limit P97.5 in normal individuals was 12.9 mg/24 h and 7.08 (mg/L)/g creatinine in first morning urine. Approximately 77% of patients with creatinine-corrected alpha-1-microglobulin > 7.08 in first morning urine, without decreased glomerular filtration or microalbuminuria, were patients with hypertension or diabetes.

Conclusion: The first urine sample of the morning can be used to quantify alpha-1-microglobulin due to its good correlation with 24-h urine samples, as well as not being affected by age or gender. A quantification > 7.08 (mg/L)/g creatinine in the first morning urine should raise suspicion of the onset of tubular damage, especially in hypertensive or diabetic patients.

RESUMEN

Palabras clave:

Alfa-1-microglobulina
Primera orina de la mañana
Albuminuria
Diabetes
Hipertensión

Introducción: La muestra de referencia para la cuantificación de Alfa-1-microglobulina es la orina de 24 horas, sin embargo, aunque habitualmente se cuantifica en la segunda orina de la mañana, es la orina de primera hora de la mañana la menos influenciada por la tasa de filtración glomerular. Así mismo, existen opiniones contradictorias sobre la influencia de la edad y el sexo en la cuantificación.

Pacientes y métodos: Se seleccionaron 434 analíticas de orina, 182 con una Tasa de Filtrado Glomerular entre 4 y 89 mL/min/1,73 m² y 252 con un Filtrado glomerular >90 mL/min/1,73 m². De estas 252, 122 correspondían a orinas de primera hora de la mañana con densidad > 1015 y 130 a orinas de 24 horas con un volumen de orina entre 400-3000 mL/24 horas, sin microalbuminuria. De las 122, 30 tuvieron un valor de alfa-1-microglobulina > 4.3 mg/L y correspondían a pacientes con enfermedades que producen daño tubular. La correlación entre la alfa-1-microglobulina de primera hora de la mañana y de 24 horas se realizó con 42 orinas, dentro de las 434 seleccionadas, que tenían solicitadas ambas muestras de orina.

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Resultados: La correlación entre la cuantificación en primera orina de la mañana y de 24 horas fue de 0,92. No se encontraron diferencias estadísticamente significativas entre Alfa-1-microglobulina corregida por creatinina con la edad, ni entre hombres y mujeres en las muestras de orina de primera hora de la mañana ni de 24 horas ($p > 0.05$). El límite superior P97.5 en personas normales fue de 12.9 mg/24 horas y de 7.08 (mg/L) / g creatinina en primera orina de la mañana. Aproximadamente el 77 % de los pacientes con Alfa-1-microglobulina corregida por creatinina > 7.08 en primera orina de la mañana, sin disminución del filtrado glomerular ni microalbuminuria, eran pacientes con hipertensión o diabetes.

Conclusiones: La primera orina de la mañana es una muestra que se puede utilizar para la cuantificación de Alfa-1-microglobulina debido a su buena correlación con la orina de 24 horas, además de no verse afectada por la edad o el sexo. Una cuantificación > 7.08 (mg/L) / g creatinina en primera orina de la mañana nos debe hacer sospechar un inicio de lesión tubular, especialmente en pacientes hipertensos o diabéticos.

Introduction

Alpha-1-microglobulin (A1M) is a 27 kDa glycoprotein produced by the liver¹; it is filtered through the glomerulus and is almost completely reabsorbed (99%) in the proximal convoluted tubules and thus is present in very small amounts in urine.² High levels of A1M in the urine suggest the presence of a proximal tubular lesion³—an early event in diabetes mellitus, even in normoalbuminuric patients^{4–7}—because a decline in renal function is better correlated with interstitial tubule damage than with the presence of a glomerular lesion.^{8–10}

The reference method for quantifying proteinuria is collection of the 24-h urine (U_{24}), but since these collections are cumbersome, the second urine of the morning is typically used. However, the glomerular filtration rate varies throughout the day,^{11–13} altering the concentration of the urine, but in the context of A1M, this problem can be solved by relating it to the amount of creatinine excreted.¹¹ That said, the first morning urine (U_{1M}) is less influenced by these factors,¹⁴ and after correction for creatinine level, U_{1M} is well correlated with the U_{24} .¹⁵

The normal value of A1M in the second morning urine used in clinical practice is < 12 mg/L, regardless of age and sex.^{16,17} However, second morning urine values have greater variability between men and women,¹⁴ and the correction for creatinine does not account for all of these differences.^{18–20} The same phenomenon can be observed with respect to age; some authors argue that the normal A1M range depends on age,¹⁸ whereas others argue otherwise.²¹

Among the diseases in which tubular damage occurs prior to chronic renal failure are type 2 diabetes mellitus (DM) and arterial hypertension (AHT), the 2 leading causes of chronic renal failure and entry into maintenance dialysis programs in Spain; therefore, it would be valuable to identify a method for quantifying A1M as a measure of tubular damage in a urine sample. Ideally, this method should not involve alterations in the A1M level throughout the day and should enable easy patient sample collection.

Thus, we chose to evaluate the possibility of using the first morning urine and correlating it with the 24-h urine, as well as to study whether there are differences in the normal values of the A1M level between men and women and with respect to age. Ultimately, we sought to establish normal values for our population and to determine whether the values of U_{1M} corrected for creatinine are elevated in

patients with diseases that involve tubular damage vs. in healthy individuals.

Materials and methods

Patients

This is an analytical observational study in which data were collected from our computer system for the years 2020–2024; subsequently, 434 analyses with available glomerular filtration rate (GFR) data and U_{1M} and/or U_{24} analyses were selected. One hundred eighty-two analyses had a GFR of 4–89 mL/min/1.73 m² and A1M quantified in O1M. The remaining 252 analyses had a GFR > 90 mL/min/1.73 m² and were classified into 2 groups: the G1T U_{1M} group, which consisted of 122 analyses with U_{1M} data and an albumin/creatinine ratio < 30 and a urine density > 1.015 , and the G1T U_{24} group, which consisted of 130 analyses with U_{24} data, urinary albumin < 30 mg/24 h and a urinary volume between 400 and 3000 mL/day.

Within the G1T U_{1M} and G1T U_{24} groups, the urine results were reviewed; urine samples with A1M levels > 4.3 mg/L were reviewed; those whose diagnosis corresponded to renal or systemic diseases that have been shown to produce tubular damage, such as DM,^{23–25} AHT,²⁶ inflammatory diseases (lupus),²⁷ chronic glomerulonephritis,²⁸ chronic renal obstruction,^{29,30} vesicourethral reflux associated with urinary tract infection,³¹ chronic pyelonephritis,³² chronic renal calculi,³³ polycystic kidney,³⁴ tubulointerstitial nephropathies³⁵ or light chain deposition diseases,³⁶ were excluded from the G1T U_{1M} and G1T U_{24} groups (corresponding to 30 and 17 urine samples, respectively) and instead included in the G1N U_{1M} and G1N U_{24} groups. Details of the groups are listed in Table 1.

The correlation between A1M in the first morning urine and that in the 24 h urine was assessed in 42 urine samples of the 434 with both values available.

Selection of variables

GFR, albuminuria, urine density, urine volume and A1M were selected as variables for defining our groups.

Table 1
Groups according to the glomerular filtration rate.

	GFR (mL/min/1.73 m ²)						
	>90		60–89	45–59	30–44	15–29	<15
	(% men/% women)						
A1M (mg/L)	G1T	G1N	G2	G3	G4	G5	G6
< 4.3 U_{1M}	90 (47/53)	90 (47/53)	54	9	1	1	0
> 4.3 U_{1M}	32 (57/43)	2 (50/50)	34	27	27	22	7
< 4.3 U_{24}	103 (42/58)	103 (42/58)					
> 4.3 U_{24}	27 (45/55)	10 (40/60)					

A1M: alpha-1-microglobulin urine; GFR: glomerular filtration rate; G1N: G1T- urine from patients with diseases that can produce tubular damage, G2, G3, G4, G5 and G6; U_{1M} : first morning urine; U_{24} : 24 h urine.

Based on the TFG, the urine samples with quantified A1M were divided into 6 groups (Table 1). Normoalbuminuria was defined as an albumin/creatinine ratio < 30 in the first morning urine³⁷ or < 30 mg of albumin in the 24 h urine.³⁸ Urine density reflects the ability of the kidney to concentrate or dilute urine, with normal values of 1.015–1.020.³⁹ Oliguria is defined as a 24 h volume of urine < 400 mL/day,⁴⁰ and polyuria is defined as a urine volume > 3000 mL/day.⁴¹ We assigned a value of 4.3 mg/L to A1M levels less than 4.3 mg/L (the detection limit provided by the manufacturer, Binding Site) to calculate the A1M level in mg/L after correction for creatinine in g/L, or as mg/24 h.⁴²

Methods

Blood samples were drawn between 08:00 and 09:00 AM and after 12 h of fasting. Serum was obtained by centrifugation at 3000 rpm for 5 min. Urine samples were centrifuged at 2000 g for 10 min. The creatinine level was determined by the Jaffé method on a Cobas® c702 autoanalyzer, and the urine albumin level was determined by an immunoturbidimetric method (Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim). The MDRD-4 equation was used to estimate the GFR.⁴³ To determine the A1M level, urine was aliquoted and stored at 2–8 °C for a maximum of 7 days, since these samples are stable up to 21 days at 4 °C.⁴⁴ The level of A1M was subsequently determined by an immunoturbidimetric assay in an Optilite® analyzer (Binding Site, Birmingham, UK). Urine density was determined in the first urine of the morning using Cobas u pack strips in the Cobas® u 601 urine analyzer (Roche Diagnostics).

Statistical analysis

Statistical analysis was performed using IBM SPSS® Statistics software version 27. The normality of the distribution of quantitative variables was evaluated using the Kolmogorov–Smirnov test. Depending on the results, parametric or nonparametric statistical tests were applied for intergroup comparisons.

For the A1M level at 24 h, the results of the Kolmogorov–Smirnov test indicated that the data did not follow a normal distribution ($p < 0.05$). Therefore, the nonparametric Mann–Whitney U test was used to compare the values between men and women. The association between A1M in urine at 24 h and age was evaluated using the Spearman correlation coefficient.

Regarding A1M in spot urine, the Kolmogorov–Smirnov test indicated that the data followed a normal distribution ($p > 0.05$). Therefore, Student's t -test for independent samples was used for

comparisons between the sexes. The correlation between A1M in the first morning urine and age was evaluated using Pearson's correlation.

Finally, for the different groups, the 97.5 percentile was used to determine the normal upper limit of the A1M level at 24 h and the A1M level in mg/L/g of creatinine in the urine of healthy individuals.

Our study was carried out in accordance with the ethical principles established in the Declaration of Helsinki. We reviewed the clinical histories of 43 patients whose urine A1M level was > 4.3 mg/L. In observational studies involving the review of the medical records of fewer than 50 patients, according to the ethics committee of our hospital, it is not necessary to request the express authorization of the patients; for this reason, informed consent was not obtained. The clinical information was anonymized, guaranteeing the confidentiality of the data at all times.

Results

The correlation between A1M U_{24} and A1M U_{1M} (mg/L)/creatinine (g/L) in first-morning urine was $r = 0.92$ (Fig. 1).

Within the G1N U_{24} group, there were no statistically significant differences between the A1M level in U_{24} between females and males ($p > 0.05$). No differences were found in the G1N U_{1M} group in the level of A1M corrected for creatinine ($p > 0.05$). With respect to age, there were no significant differences between the values of A1M and age in the G1N U_{24} and G1N U_{1M} groups ($p > 0.05$) or between the A1M levels of males and females with respect to age within these 2 groups (Fig. 2).

Within the G1N groups, most A1M levels were < 4.3 mg/L (lower limit of detection provided by the manufacturer, Binding Site): 97.8% for U_{1M} and 91.5% for U_{24} (Fig. 3).

The upper limit $P_{97.5}$ for the A1M level in the G1N U_{24} group was 12.9 mg/24 h, and for the G1N U_{1M} group, it was 7.08 A1M mg/L/g creatinine.

Among the 30 urine samples from the G1T U_{1M} group with an A1M level > 4.3 mg/L, 19 were from patients diagnosed with hypertension and/or DM, and 11 were from patients with other diseases that can produce tubular damage. When corrected for creatinine, the A1M level was > 7.08 mg/L/g creatinine in 18 samples (14 from subjects with AHT and/or DM and 4 from subjects with other diseases that produce tubular damage) (Fig. 4). Statistically significant differences were observed between the means of the A1M level corrected for creatinine in the G1N U_{1M} group and those of these 18 urine samples.

According to these results, in the G1T group, an A1M level > 7.08 mg/L/g creatinine can predict tubular damage with a positive

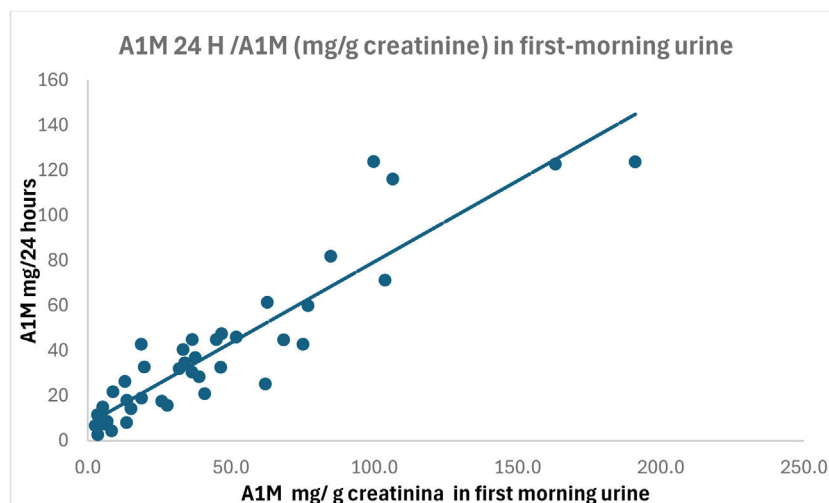


Figure 1. Correlation of the A1M level in the 24 h urine and the first-morning urine.

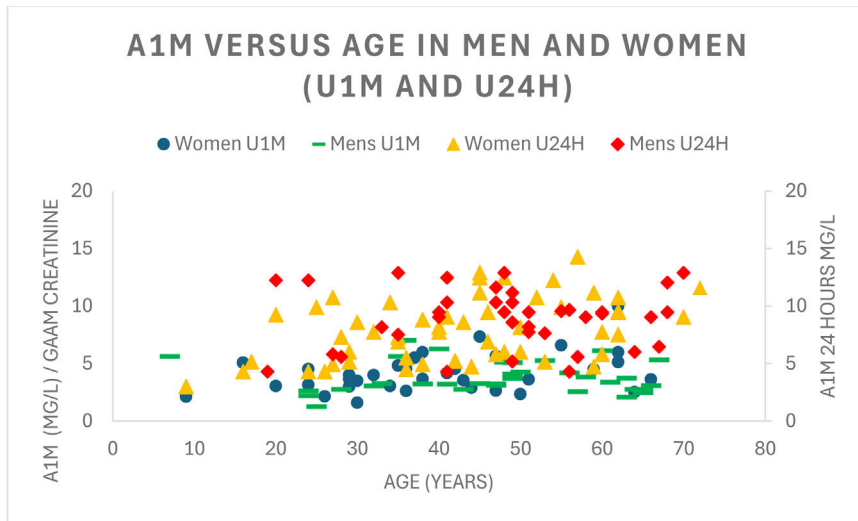


Figure 2. U_{1M}: first-morning urine of the G1N group; U₂₄: 24 h urine of the G1N group.

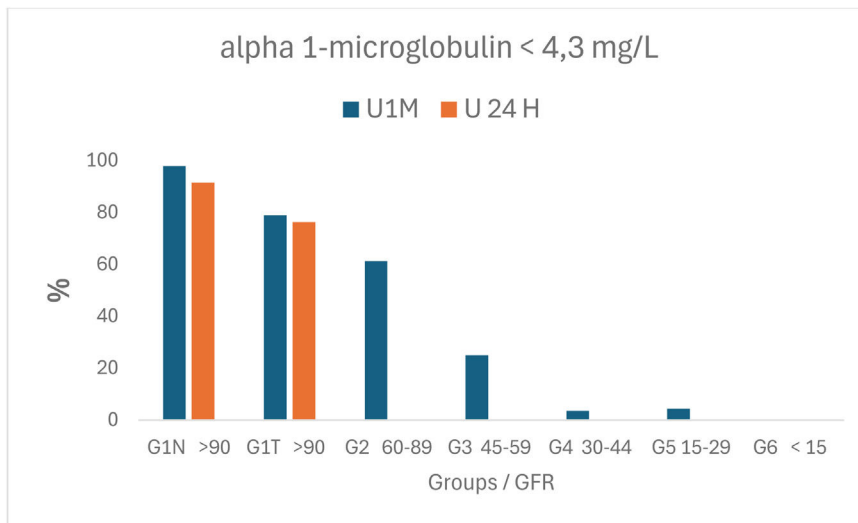


Figure 3. U_{1M}: first-morning urine; U_{24H}: 24 h urine; GFR: glomerular filtration rate.

predictive value (PPV) of 90% and a negative predictive value (NPV) of 88%.

Discussion

As shown in Fig. 1, a strong correlation was observed between the A1M level in U_{1M} after correction for creatinine and the A1M level in 24 h urine (r: 0.92). In addition, we did not find statistically significant differences between the A1M values in U₂₄ of men and women (G1N U₂₄ group) or between the A1M values corrected by creatinine in the first morning urine of men and women (G1N U_{1M} group).

With respect to age, we did not observe a significant correlation for the A1M in the G1N U₂₄ group or for the A1M corrected for creatinine in the G1N U_{1M}; moreover, we did not observe a significant correlation between females and males with respect to age in these 2 groups.

Taking into account the good correlation of A1M between U₂₄ and U_{1M} of the G1N U₂₄ and G1N U_{1M} groups and that U_{1M} is less influenced by factors that can cause greater variability in the results, such as the urine of the second morning urination or another diurnal random sample,¹⁵ evaluating tubular function with the first morning urine sample would be more logical. We must also consider that the

first urine of the morning is typically used for determinations such as dipstick tests, pregnancy tests, urine culture and quantification of the albumin/creatinine ratio; thus, if we use this sample for the determination of A1M, the patient should not have to collect a second unnecessary sample. As shown in Fig. 3, 97.8% of the samples from the A1M U_{1M} group and 91.5% of those from the A1M U₂₄ group had an A1M value < 4.3 mg/L; that is, the levels were below the detection limit of the technique given by the manufacturer (Binding Site), which indicates that the vast majority of normal people should not have A1M detected in urine, since if the tubules function properly, it is almost completely reabsorbed (99%).² The P_{97.5} in the G1N U₂₄ group was 12.9 mg/24 h, and the P_{97.5} in the O1N U_{1M} group was 7.08 A1M mg/L/g creatinine; these values are very similar to those reported by Everaert et al.¹⁸ (5.0 (2.4–8.0) A1M mg/L/g creatinine).

Group G1T, with a GFR > 90 GFR (mL/min/1.73 m²), no microalbuminuria and a urine density > 1.015, differed from the G1N group in 30 urines with an A1M value in U_{1M} > 4.3 mg/L, indicating that these patients had diseases that caused tubular damage. Among these 30 patients, 19 had hypertension and/or DM with more than 10 years of evolution; when corrected for urinary creatinine, 14 had values > 7.08 A1M mg/L/g creatinine (8.5–40.8 A1M mg/L/g creatinine). Another 11 urine samples were from

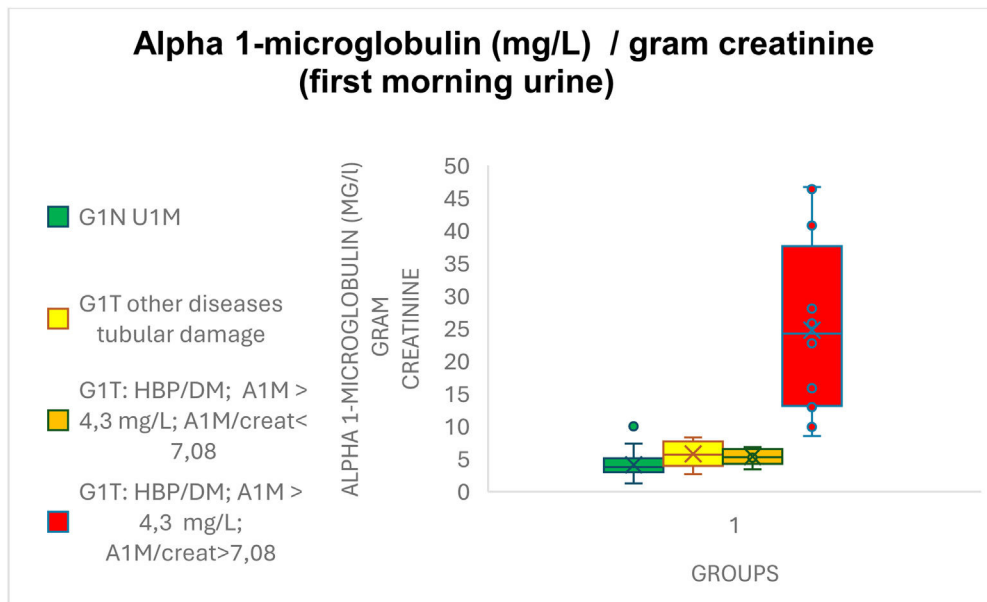


Figure 4. G1N group (G1T- diseases that produce tubular damage); A1M: alpha-1-microglobulin; DM: diabetes mellitus; AHT: arterial hypertension; U_{1M}: first-morning urine.

patients with other diseases that can cause tubular damage; when corrected for creatinine, 4 had values > 7.08 A1M mg/L/g creatinine (7.2–8.3 A1M mg/L/g creatinine). The mean of these 18 urine samples with A1M values corrected for creatinine > 7.08 differed significantly from the mean of A1M corrected by creatinine of Group G1N U_{1M}.

Thus, an A1M corrected for creatinine > 7.08 A1M mg/L/g creatinine can reveal incipient tubular damage with a 90% PPV, especially in diabetic and/or hypertensive patients, since approximately one-third of patients present alterations in their renal function, deterioration that is accentuated over time. of the years being doomed to nephrosclerosis and diabetic nephropathy.²² Therefore, it is important to consider the renal function of these patients from the time of disease diagnosis and quantify A1M in first morning urine, especially in patients with a normal GFR and no microalbuminuria, which will result in stricter control of these patients. and a decrease in the risk of progression to chronic kidney disease, as well as the occurrence of cardiovascular events.

Limitations of the study

This study was designed to obtain normal values of A1M in first morning urine. The relationship between A1M U_{1M} corrected for creatinine and diseases that produce tubular damage would require a more exhaustive study with a larger number of samples.

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Declaration of competing interest

The authors declare that there are no conflicts of interest or of any other type.

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