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ORIGINAL ARTICLE

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Urea percentiles in children with chronic renal failure

Data from the ItalKid project

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Abstract In chronic renal failure high serum urea levels (sUrea) are correlated with the onset of uremic symptoms. Urea has generally been considered relatively non-toxic, functioning more as a surrogate for other toxic solutes; however, it has been recently reported that it can contribute to uremic toxicity. Clinically sUrea are often difficult to interpret because of the wide range of kidney functions. To obtain a practical and easily accessible tool to evaluate sUrea, we have produced percentile curves for different ranges of chronic renal failure, defined with creatinine clearance (C_{Cr}) obtained with the Schwartz formula. Data were obtained from the Italian Pediatric Registry of Chronic Renal Failure (ItalKid); its inclusion criteria are: (1) C_{Cr}<75 ml/min per 1.73 m^2, (2) age <20 years at time of registration, and (3) conservative treatment. To obtain the percentiles, the following patients were excluded: patients with an underlying disease, a concomitant treatment, or a disor-

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der that could affect urea metabolism, per se, and/or food intake, and patients aged <2 years. The study group included 690 subjects (mean age 9.56±4.54 years, 485 males). In total, 2,085 observations (C_{Cr} and sUrea) were available for the construction of the percentile curves. A median of 258 (range 99–380) observations was obtained for each of the eight different categories of C_{Cr} (intervals of 10 ml/min per 1.73 m^2). The 10th, 25th, 50th, 75th, and 90th percentiles were calculated and a graph was produced. Patients with the highest urea percentiles showed significantly higher plasma levels of phosphorus and parathyroid hormone and significantly lower hemoglobin concentrations and bicarbonate levels. Our percentile curves may help to identify subjects with inappropriate sUrea for a given C_{Cr}.

Keywords Serum urea concentrations · Urea percentiles · Chronic renal failure · Protein intake

Introduction

The impairment of renal function results in various clinical abnormalities, related to progressive loss of renal metabolic and homeostatic functions. Urea metabolism is severely affected by renal failure as, for a given nitrogen intake, serum urea (sUrea) rises roughly in parallel with the fall of glomerular filtration rate (GFR) and no significant renal tubular adaptation for urea excretion is present [1].

It has been suggested that there is a correlation between the rise in sUrea and the development of uremic symptoms, such as weakness, malaise, and bleeding due to platelet dysfunction, clinically and in animal models [1, 2, 3]; despite this suggestion, urea has generally been considered relatively non-toxic, functioning more as a surrogate for other toxic solutes [4, 5]. The potential role of sUrea in the syndrome of uremia has recently been reevaluated. Cell culture studies have suggested that elevated levels of urea may contribute to the accelerated atherogenesis frequently seen in patients with renal failure, by increasing macrophage proliferation and inhibiting macrophage apoptosis [6, 7]. It has also been reported that the impairment of protein function, secondary to high urea concentrations, is offset by the accumulation of other low molecular weight osmolytes: the methylamines [8].

In the growing organism protein intake is, per se, of the utmost importance, as normal growth requires a minimum quantity of protein [9]. On the other hand, it has been proposed that limiting protein intake might slow the progression of renal damage, because dietary protein intake is responsible for hyperfiltration [10].

Repeated evaluations of nitrogen balance would be the most accurate way to predict the metabolic status of a child, but they are time consuming and laborious in the routine clinical setting; sUrea is normally measured, but reference data only identify an upper normal value and not a range for different GFR values.

Using a large database (Italian Pediatric Registry of Chronic Renal Failure), we have produced percentile curves of sUrea for different creatinine clearance levels (C_{Cr}), for the age group 2–20 years. These percentiles may help to identify the children with inappropriate sUrea for a given GFR. Nitrogen balance studies will clarify the meaning of high sUrea in single patients.

Patients and methods

Data were obtained from a pediatric nationwide (Italy) population-based registry of patients with chronic renal failure (CRF) on conservative treatment (ItalKid). This registry began its activity in 1990. The inclusion criteria are as follows: (1) C_{Cr} (Schwartz formula) [11] <75 ml/min per 1.73 m^2, (2) age <20 years at time of registration, and (3) conservative treatment. Once the patient has been registered, follow-up continues until the beginning of renal replacement therapy. A form is sent to the participating centers every year, in order to update the clinical and biochemical data for each subject. Collected data refer to the last visit before 31 December of each year. A total of 127 centers have reported cases that have been registered. There were 1,195 patients stored in the database on 31 December 2000. Written informed consent to collect, report, and store the information is obtained from the patients and/or one of their parents.

Patients

Patients were selected on the basis of the following exclusion criteria: (1) children with diseases that could significantly affect urea metabolism per se, such as metabolic diseases (methylmalonic acidosis, diabetes mellitus); (2) patients with any disease that could benefit from steroid treatment, who could have been taking such drugs (lupus, vasculitis, glomerulonephritis, etc); (3) patients with concomitant conditions that could affect nutritional balance and/or food intake, such as heart or liver disease or muscular dystrophy, neoplasias, severe mental retardation, or associated syndromes; (4) age younger than 2 years, because of the different protein and calorie intake.

A total of 690 subjects (485 males, 70.3%, and 205 females, 29.7%, mean age 9.56±4.54 years) constituted our study group. The primary causes of CRF were: renal hypo-dysplasia associated with major urological malformation (373), isolated renal hypodysplasia (119), neurogenic bladder (24), cortical necrosis (56), nephronophthisis (31), polycystic kidney disease (30), hemolytic uremic syndrome (29), interstitial nephritis (23), and Alport syndrome (6).

Biochemical data

After 10 years of registry activity a total number of 2,085 observations [C_{Cr} (Schwartz formula [11]) and sUrea] were available to construct the percentile curves, with a median number of 3 (range 1–9) observations per patient.

In order to evaluate the metabolic status of patients with CRF at different urea levels, 1,915 simultaneous measurements of C_{Cr}, sUrea, calcium, phosphorus, hemoglobin concentrations, and base excess were available. A total of 906 measurements of parathyroid hormone (iPTH) were also available.

Urea percentiles

C_{Cr} was divided into eight different categories. The lowest C_{Cr} group comprised between 5 and 10 ml/min per 1.73 m^2, a 10 ml/min per 1.73 m^2 interval was then used to form the other seven groups from 10 to 80 ml/min per 1.73 m^2 (e.g., category 15

contained C_{Cr} values between 10 and 20). The highest C_{Cr} category (75) was constructed using data of patients who showed an increase (up to 80) of C_{Cr} after entering the registry. In effect, the inclusion criteria of the registry excluded children with C_{Cr}>75. The 2,085 sUrea values were then allocated to the corresponding C_{Cr} category and utilized to build the percentiles.

Quality control of data

A quality control survey involving a sample of 20% of the laboratories of the participating centers (covering more than 80% of registered patients) was undertaken in order to ensure that the definition of CRF based on sCr and urea levels, as determined locally, was reliable. At sCr levels of 0.86, 1.95, and 3.44 mg/dl, the observed coefficients of variance (CVs) were 13.0%, 7.6%, and 6.0%, respectively; at sUrea levels of 34.9, 84.4, and 142.9 mg/dl, the observed CVs were 4.8%, 3.7%, and 3.6%, respectively.

Statistical methods

Data are reported as mean±SD or median and range as appropriate. The percentile curves were obtained with Stat View 5.0.1 statistical package. Comparisons within different groups were made using ANOVA and the Kruskal-Wallis test for parametric and non-parametric variables, respectively. The general linear model was used to assess the simultaneous independent role of C_{Cr}, sex, and age on urea values. In this analysis, urea values were the dependent variable. P<0.01 was considered statistically significant.

Table 1 Serum urea values in relation to the calculated percentiles and the corresponding creatinine clearance (C_{Cr}) intervals

C_{Cr} (ml/min per 1.73 m^2)	Serum urea levels (mg/dl) and related percentiles					
	10th	25th	50th	75th	90th	*n*
5.0–9.9	97	138	179	232	274	99
10.0–19.9	77	100	136	166	194	258
20.0–29.9	48	71	99	124	151	263
30.0–39.9	42	60	77	97	116	234
40.0–49.9	36	55	64	80	98	255
50.0–59.9	29	40	52	62	75	312
60.0–69.9	29	36	45	54	62	380
70.0–79.9	29	35	41	48	58	284

Table 2 Effect of C_{Cr} on urea values adjusted for possible confounding factors by multivariate analysis

Variable	*F*	*P*
Age	28.1	<0.001
Sex	2.2	0.1364
Creatinine	4.9	0.0280
Proteinuria	12.9	<0.001

Results

sUrea values were homogeneously distributed among the different C_{Cr} classes: mean 260, range 99–380. The lowest class, which has a narrower range of renal function (5 ml/min) compared with the other classes that have a range of 10 ml/min, comprised 99 observations. The 10th, 25th, 50th, 75th, and 90th percentiles for sUrea were then calculated. The corresponding values are summarized in Table 1. As expected, sUrea was directly associated with age. Multivariate analysis shows that C_{Cr} has an independent, significant effect on urea values, after adjusting the data for other possible confounding variables, such sex and age (Table 2).

The graph, which depicts the urea percentiles, on the basis of C_{Cr}, is shown in Fig. 1. The range of sUrea increases with the worsening of kidney function, showing a higher variability in children with a more severe chronic renal insufficiency. The hematological and biochemical parameters were stratified according to sUrea quartiles (Tables 3 and 4): 1. low (<25th percentile); 2. low-moderate (25th-50th percentile); 3. high-moderate (50th-75th centile); 4. high (>75th percentile). By definition, the four categories have the same C_{Cr}. No significant dif-

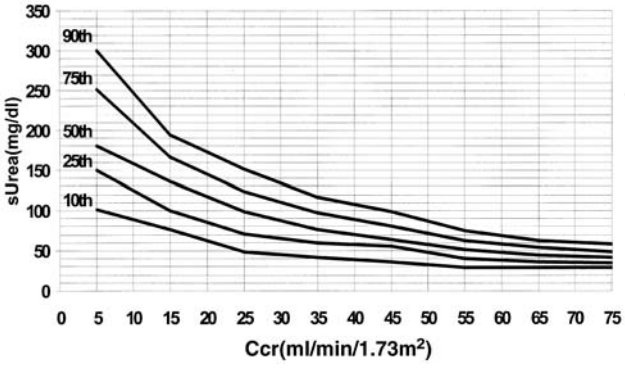

Fig. 1 Urea percentile curves in children with chronic renal insufficiency

Table 3 Biochemical and hematological parameters in relation to the corresponding serum urea percentile (*Ca* calcium, *P* phosphorus, *Hb* hemoglobin, *BE* base excess)

Serum urea	*n*	Urea (mg/dl)	C_{Cr} (ml/min per 1.73 m^2)	Age (years)	Ca (mg/dl)	P (mg/dl)	Hb (g/dl)	BE (mmol/l)
Low	524	46.0 (23.2)	43.8 (20.2)	8.6 (4.49)	9.82 (0.64)	4.70 (0.79)	12.3 (1.6)	–1.95 (2.75)
Low-moderate	454	66.3 (29.7)	45.5 (19.5)	9.70 (4.72)	9.83 (0.53)	4.70 (0.78)	12.3 (1.7)	–1.55 (2.69)
High-moderate	490	84.4 (40.6)	44.1 (20.2)	10.03 (4.64)	9.81 (0.56)	4.84 (0.83)	12.1 (1.9)	–1.94 (2.65)
High	447	113.2 (57.2)	43.9 (19.9)	10.21 (4.20)	9.80 (0.57)	5.03 (0.91)	11.9 (1.7)	–2.90 (3.34)
P (ANOVA)			NS	<0.0001	NS	<0.0001	<0.001	<0.0001

Values are expressed as mean and (SD). Low <25th percentile; low-moderate 25th–50th percentile; high-moderate 50th–75th percentile; high >75th percentile

Table 4 Intact parathyroid hormone (iPTH) values in relation to the corresponding blood urea percentile

Serum urea	*n*	iPTH (ng/l)
Low	217	48.0 (4–778)[a]
Low-moderate	226	46.5 (1–1,700)[b]
High-moderate	255	58.0 (1–1,010)[c]
High	208	65.0 (7–1,673)[d]
P		a, b vs. d <0.001

iPTH values are expressed as median and range; low <25th percentile; low-moderate 25th–50th percentile; high-moderate 50th–75th percentile; high >75th percentile

ference in age was observed among the groups, except for the low urea group whose mean age was significantly lower than in the other groups. The patients with the highest sUrea also showed the highest values of phosphorus and PTH, and the lowest hemoglobin levels and bicarbonate concentrations (levels of significance are provided in Tables 3 and 4). Serum calcium levels did not show any significant difference amongst the four groups.

Discussion

Urea is the major end product of protein catabolism; its potential intrinsic toxicity was recognized by Richard Bright for the first time in 1831 [12]. Nevertheless, its definite role in uremic toxicity has never been established [4, 5, 6, 7, 8], despite the ubiquity of urea kinetic modeling (Kt normalized or not to total body water, V) as a measure of dialysis therapy [13, 14]. In a prospective cohort study in adults [15], patients with higher interdialytic urea levels were hospitalized more often, had more severe neurological symptoms and an increased morbidity. Urea might just therefore be an easily measurable and reliable marker of the retention of other unidentified low molecular weight toxins, which could contribute to the well-known uremic symptoms and to the metabolic disturbances associated with CRF.

Urea concentration in the blood is determined by the rate of urea synthesis, the rate of urea clearance, and the volume of distribution of urea. In CRF the increase of sUrea is proportional to the progression of the disease, but it is highly influenced by a catabolic state or an excessive protein introduction, leading to a higher production of other waste substances of protein catabolism.

In children with CRF the evaluation of metabolic balance has to take into consideration the higher anabolism, secondary to growth. A balance has to be achieved between sufficient protein intake to guarantee adequate growth and satisfactory metabolic control. Identifying a catabolic status or an excessive protein intake is therefore important, but may be difficult. sUrea is routinely measured in the clinical setting, but reference data only identify an upper normal value and not a range for different GFR values. Our percentiles provide a reference that can obviate the difficulty in interpreting sUrea. We do not advocate that they replace nitrogen balance studies, but we are sure that they represent an additional useful tool. Furthermore, they are very easy and quick to use, and may help to continuously monitor our children with CRF. Nitrogen balance studies will then help to understand why sUrea is elevated.

The association between a high sUrea and poor metabolic control is suggested by significantly higher values of phosphorus and iPTH and lower hemoglobin and bicarbonate levels (Tables 3 and 4). The lower base excess in children with high urea concentrations may mean either that protein waste products, generated by high protein intake or catabolism, worsen acidosis per se or that acidosis promotes catabolism and thereby production of urea. The observed differences in phosphorus, iPTH, hemoglobin, and bicarbonate levels might seem of modest clinical importance; however, it should be stressed that they represent the mean of a very large number of observations, which include many patients with mild renal impairment.

Children who do not comply with dietary recommendations, may also be less compliant with pharmacological therapy. This could also explain the high sUrea, phosphorus, and iPTH levels. However, the percentiles can also help to identify those patients with inappropriately high sUrea, secondary to low diuresis, related to relative dehydration. There is a recognized influence of urinary flow rate on urea clearance, due to variable urea reabsorption in the distal nephron. An increase in vasopressin dramatically reduces the clearance and the excreted fraction of urea, by decreasing urinary flow rate. The consequent elevations of sUrea are usually combated by increases in GFR, which are less efficient in patients with CRF [16].

To the best of our knowledge there are no percentile curves for sUrea reported in the adult and pediatric literature. These percentiles describe the actual distribution for any given C_{Cr} level in the Italian pediatric CRF population, after possible effects on sUrea of drugs or associated conditions and co-morbidities affecting protein metabolism had been eliminated. It is beyond our scope to define the optimal range of azotemia, but levels higher than the 75th percentile can reasonably identify those patients with poor metabolic control or an excessive protein intake. The clinician can utilize these percentiles to evaluate the level of azotemia for a given C_{Cr} and its progression in the same patient more objectively, independent from any worsening of renal function.

The set of percentiles presented here are limited to the age range 2–20 years, because growth is particularly pronounced during the first 2 years of life and the dietary requirements of small children below 2 years of age differ considerably from those of other age groups.

In conclusion, the large number of patients and measurements considered has allowed the construction of sUrea percentiles as a function of C_{Cr}, which are representative of a pediatric population with renal failure. Blood urea values >75th percentile suggest the need for careful evaluation of a possible catabolic status.

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