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On the Urinary Excretion of a Substance as Predicted from the Substance-to-Creatinine Ratio

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Abstract: Equations predicting the urinary excretion of a substance of interest have been developed from a deterministic model linking substance-to-creatinine ratio with expected creatinine output for sex and age. Developed predictive equations show ≥ 80% accuracy and ≥ 90% agreement with traditional, established methods recurring to 24 hours urine collections. Clinical usefulness of the predictive equations has been validated in the study of calcium metabolism disorders. Predictive equations can be expanded to accommodate the specific gravity and osmolarity of urine. Predictive equations discussed in this essay have opened new windows in the assessment of kidney function and metabolic disorders. It is expected these predictive equations to secure a higher compliance of kidney assessment tests in children and adolescents.

Keywords: Substance-to-Creatinine Ratio, Creatinine, Diagnostic Agreement, Analytical Accuracy, 24 Hours Urine

1. Introduction

The assessment of the kidney function offers valuable data on the regulation of the internal milieu and the utilization of nutrients by cells, tissues and organs [1-3]. However, conduction of kidney assessment tests is affected by shortcomings surrounding the collection of a volume of urine representating a day in the subject's life. An accurate 24 hours urine collection demands a great deal of commitment and disposition by patients and health care workers alike. In the best of cases, response rate to 24 hours urine collection orders is less than 50%, and only a third of all these collections proves to be accurate [4-5]. Besides, obtained results might represent past instead of current events [6]. Solutions so far fostered for circumventing 24 hours collections have been found to be ineffective and short-lived [7-8].

The substance-to-creatinine ratio * assayed in a urine morning sample has been advocated in several clinical scenarios as a surrogate of the urinary excretion of the substance in question [9-11]. The albumin-to-creatinine ratio for assessing kidney function of hypertensive and diabetic patients [12], and the calcium-to-creatinine ratio in the study of disorders of calcium metabolism and stones-forming diseases [13-15], are just two examples of such surrogates.

The authors have incorporated IndEx into a deterministic model in order to allow the estimation of the excretion of a substance of interest as a function of the child's sex, age, height and body surface area (BSA) [16-17]. What follows is the presentation of this deterministic model, along with examples of its application in the authors's hospital.

2. Methods

2.1. Presentation of a Deterministic Model for Estimating the Urinary Excretion of a Substance

The urine content of a substance of interest in an accurate 24 hours urine collection † can be expressed by a mathematical function linking *IndEx* with the expected 24 hours creatinine output:

* From heretofore regarded as *IndEx*.

† From heretofore denoted by *ExMet*.

$$\text{ExMet, g.24 hours}^{-1} = \text{IndEx, g/g} * \text{OCre}_{\text{expected}}\text{, g.24 hours}^{-1} \quad (1)$$

$$\text{ExMet, g.24 hours}^{-1} = \frac{\left[Subst, g.L^{-1}\right]}{\left[OCre_{assayed}, g.L^{-1}\right]}\text{, g/g} * \text{OCre}_{\text{expected}}\text{, g.24 hours}^{-1} \quad (2)$$

The expected 24 hours creatinine output can be approximated from a transformation of the Schwartz's equation used for calculating the child's glomerular filtration rate (eFG):

$$\text{eFG, mL.minute}^{-1} \textit{ per } 1.73 \text{ m}^{-2} \text{ BSA} = Q * \frac{\left[Height, cm\right]}{\left[SCre_{assayed}, mg.dL^{-1}\right]} \quad (3)$$

Constant Q depends upon the child's age: Q = 0.45 for ages < 1 year; Q = 0.50 otherwise.
Then:

$$\text{OCre}_{\text{expected}}\text{, g.24 hours}^{-1} = \text{Height, cm} * \text{BSA, m}^{-2} * Q * U \quad (4)$$

Hence:

$$\text{ExMet, g.24 hours}^{-1} = \frac{\left[Subst, g.L^{-1}\right]}{\left[OCre_{assayed}, g.L^{-1}\right]}\text{, g/g} * \text{Height, cm} * \text{BSA, m}^{-2} * Q * U \quad (5)$$

In the above expression U = 0.00833 if analyte's mass is given in grams.24 hours^{-1} (U = 8.33 otherwise).

As developed, the model in [5] does not rely upon a 24 hours urine collection, thus allowing fast and immediate results. Besides, the model developed in [5] is deterministic in its nature inasmuch as the urine excretion of the substance of interest can be modeled from its *IndEx* expressed as a fraction of the creatinine output expected in 24 hours.

2.2. Statistical Validation of the Developed Model

Several works completed by the authors have presented the results of extensive statistical validation of the predictive models following [5] advanced for analytes of interest such as total proteins, albumin, calcium, urates and magnesium [16], [17]: a required step before introducing them into clinical practice. Overall, an analytical accuracy ≥ 80% (estimated from the determination r^2 coefficient of the intermethod-comparison straight line) was achieved with the developed model, rendering the predictive equation suitable for diagnostic purposes [18]. The slope of the intermethod comparison straight line ranged from 1.1100 (total proteins) to 0.7057 (magnesium) [18]. However, slopes estimates might be affected by the nature of the statistical method used for data analysis, the analytical range of measurements, and the (disproportionate) presence of abnormal, pathological values. Intermethod agreement (given by the fraction of those correctly classified with both methods) was (on the average) ≥ 90%.

Table 1. *Analytical validation of the predictive equations for 5 analytes measured in children and adolescents developed after the deterministic model presented in box [5].*

Analyte	r^2	Slope	Agreement
Total proteins	0.9762	1.1100	96.8
Albumin	0.9974	0.9636	93.3
Calcium	0.9074	0.9783	89.0
Magnesium	0.8445	0.7057	Not estimated
Urates	0.8874	0.8594	90.0

Data taken from: Reference [16].

2.3. Clinical Validation of the Developed Model

Validation of a diagnostic method is also a clinical task: new methods should produce clinical results in agreement with mainstream literature [19]. However, the clinical validation of a new diagnostic method demands a perfectly delimited clinical setting where both the reference (also referred as the currently used) and the alternative (also denoted as the proposed) methods can be applied proficiently to the same subjects (already independently sampled with a reference or a "gold standard" method) in order to judge their clinical validity.

So far, the best clinical example of the usefulness of the model described here (and in other articles) refers to the use of the calcium-to-creatinine ratio in the assessment of non-glomerular hematuria (concurring or not with kidney lithiasis) in children and adolescents assessed at the author's laboratory [20]. Kidney lithiasis might affect 1% of Cuban children and adolescents [21]. However, data is scarce on the frequency of hypercalciuria in these subpopulations [22], perhaps due to aforementioned shortcomings surrounding the measurement of 24 hours calciuria. In a serie of +1,000

children and adolescents with kidney lithiasis assisted at the Institute of Nephrology of Havana, abnormally elevated 24 hours calcium values were seen in a third of them [23]. According to a study serie presented by the authors in a previous report [20], hypercalciuria might be present in 60% of patients with kidney lithiasis and in 68% of those ones with nonglomerular hematuria, but in 73.3% of those with both symptoms.

A follow-up, retrospective study has been completed by the authors in order to explore the associations between serum calcium values and 24 hours calciuria [24]. As expected, hypercalciuria was present in almost half of children and adolescents having elevated serum calcium values, but also in a quarter of those ones having a normal serum calcium [24].

The *IndEx* paradigm has been also used in a recently completed study on the behavior of the 24 hours uricosuria in 52 obese children and adolescents [25]. Elevated 24 hours uricosuria was present in half of the study serie, but those with one (or more) manifestation (s) of the Metabolic Syndrome (such as blood hypertension, Diabetes mellitus and/or dyslipidemias) sustained higher 24 hours uricosuria values [25].

2.4. Extensions of the Predictive Model

The predictive equations as described in this essay rely on the creatinine content determined in the urine morning sample as the *IndEx* denominator. The urine creatinine output reflects the subject's skeletal muscle mass, and by the extension, the endogenous rate of creatinine appearance. However, several factors might affect the accuracy of the measurement of the urine creatinine content, among them, the analytical procedure (colorimetric *vs*. enzymatic methods), the subject's hydration status (dehydration *vs*. overhydration), the size of the skeletal muscle mass (obesity *vs*. undernutrition and wasting), and body deformities and limb amputation, to name just a few of them [26-28].

Whatever the cause, *IndEx* can still be constructed for a specified subject using urine specific gravity (SG) instead. *IndEx* can then be estimated from the substance-to-specific gravity index thus calculated after correcting for the subject's BSA [29]. The authors have also found a statistical relationship between urine SG and its creatinine content [30]. Hence, urine creatinine content can be estimated from the sample's SG, and then used as the *IndEx* denominator [30]. Similar considerations can also be made for the urine's osmolarity.

3. Conclusions

Shortcomings surrounding collection of accurate 24 hours urine collections have made researchers and physicians to abandon (or at least not considering incorporating into their work) studies relying on the urine excretion of substances. Instead, they tend to rely (heavily most of the times) on serum measurements when studying the metabolism of substances. Use of *IndEx* values might have been an intermediate solution, but there is still a need (still unresolved) to accommodate quantities of the substance of interest appearing in urine within a 24 hours timeframe. According with the *IndEx* paradigm developed by the authors, excretion of a substance could be regarded as a fraction of the subject´s expected creatinine output, thus allowing for its expedient measurement. Excretion estimates of substances obtained by means of the developed deterministic model are accurate enough to serve diagnostic as well as research purposes. Work is under way at the authors´s lab in order to open new possibilities for the *IndEx* paradigm in the laboratory assessment of kidney disorders and other chronic conditions.

Appendix

A calculator offering the calculations described in this essay is available *on-line* at: http://nefrocalc.sarhugo.com. An application for mobile devices is also available for interested readers at: http://nefrotoolbox.sarhugo.com/.

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