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EDITORIAL COMMENTARY

What to do with kidney length and volumes in large individuals?

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Abbreviations

BSA Body surface area
ECV Extracellular volume
GFR Glomerular filtration rate
IBW Ideal body weight

Introduction

In a recent article in *Pediatric Nephrology*, Pierluigi Marzuillo et al. from Universita degli Studi della Campania Luigi, Vanvitelli, Italy, describe their work on how to assess kidney length in children and adolescents who are overweight or obese, based on height versus body surface area [1]. Marzuillo et al. evaluated kidney length in a cross-sectional study of 744 apparently healthy children (mean age 8.3 years) with a high overweight and obesity rate of 34.5%. They point out that body surface area (BSA)-based kidney length percentiles misdiagnose small kidneys in large patients and showed that unnecessary studies occur if the percentiles based on BSA are used. Marzuillo et al. conclude that only height percentiles should be used. Their work raises interesting questions about the shortcomings of our current approach. One of our co-authors (GF) received a clever electronic consult through the Ontario Telemedicine Network from Dr. John Ihnat, a family physician from Toronto, who inspired this editorial by pointing out that kidney length *and* kidney volume are often enlarged without any apparent pathology.

The paper by Marzuillo et al. [1]

Marzuillo et al. compared kidney length using age-based, height-based, and BSA-based reference intervals in Italian children [2]. The normative values were derived from 1782 European Caucasians aged 0–19 years and Box Cox transformation was used to develop LMS percentile curves and tables for kidney length, but unfortunately not for kidney volume [2]. In Marzuillo's study, the age- and height-based percentiles were significantly higher than the BSA-based percentiles for the entire group, including the overweight and obese children, which is a very interesting finding demonstrating the importance of external validation. Moreover, the reference intervals were derived from Polish and Lithuanian children, who are taller than Italian children [3]. Marzuillo's group also measured kidney function and provided a cost analysis for the often unnecessary workup if the kidney length was below the third percentile for BSA. They found that only height-based kidney length, but not BSA-based kidney length, accurately predicted impaired eGFR. They concluded that BSA-based percentiles can underestimate kidney length in overweight and obese children and that only height-based percentiles should be used.

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The problem with using a regression line outside of the range it was generated from

We commonly use the Du Bois and Du Bois formula [4] or the Mosteller formula [5] for the calculation of BSA. The Du Bois and Du Bois formula was published in 1916 and the Mosteller's formula, "a simplified calculation of BSA in metric terms," is a mathematical recalculation of older data that was published in the *Lancet* as a short correspondence in 1987 without details about the data that were used [5]. Over the past century, adult height has increased substantially and unevenly globally. In a population-based study of 1472 people born between 1986 and 1996 in 200 countries, the Non-Communicable Disease Risk Factor Collaboration Group reported a 20.2-cm gain in South Korean women and a 16.5-cm gain in Iranian men over 100 years, while men in European countries such as the Netherlands and Denmark surpassed 182.5 cm [3]. This has a substantial impact on the accuracy of BSA estimation, as all regression-based formulae only work well in patients with similar characteristics from which they are generated [6, 7]. For instance, less than 30 patients from the large CKD-Epi study were younger than 30 years, which is why the CKiD U25 formula, with more representation of younger participants, is recommended to estimate glomerular filtration rate (eGFR) for young adults [8]. In 1978, Haycock addressed the temporal height changes by revising the regression-based BSA in a study of only 81 participants: BSA = weight (kg) 0.5378 × height (cm) 0.3964 × 0.024265 [9]. The purpose was the increasing underestimation of BSA with the Dubois formula. However, population-based heights have since increased even more. Given the inaccuracy of regression-based formulae in populations with characteristics different from which the formulae are derived, the marked increase in population heights undermines the accuracy of older BSA formulae in the current scenario [10].

The added problem of obesity

We also are witnessing an obesity pandemic [11]. Since the actual weight goes into the formula for the estimation, regardless of which formula is used, it increases the BSA estimation. For normalization of the GFR, indexing BSA to 1.73 m^2 has been in place since 1928 [12] and the ideal body weight (IBW) rather than the actual body weight is recommended [13, 14]. The Traub formula published nearly 30 years ago is rarely used in clinical practice for the calculation of the ideal weight, namely IBW(kg) + 2.396$e^{0.01863}$ × height (cm) [15]. However, obesity rates have been increasing exponentially since Traub's formula was published. As of 2019, it is estimated that over 150 million children in the world are obese, and that this figure will increase to 206 million in 2025 [16]. There is ongoing discussion on which method to use, but the Traub equation only requires the height in addition to IBW and is therefore the simplest [17].

Kidney volumes versus kidney length?

Kidney volume estimation has evolved as a non-invasive tool for the estimation of kidney nephron endowment [18–21]. Kidney volumes are related to BSA and can be conveniently estimated using the approach by Scholbach and Weitzel [22]. There is even an app available that allows for bedside kidney volume and kidney length *z*-score determination (Ped(z), https://pedz.de/de/pedz/main.html, accessed 6 Nov 2022). Kidney volumes are better than kidney length [23]. Furthermore, kidney length *z*-scores can also be used to assess chronic kidney disease (CKD) progression [24]. As outlined above, there are newer values of kidney length derived from Lithuanian and Polish children available that reach current European heights [2].

What is the best way to estimate kidney volumes?

Theoretically, using the BSA based on actual rather than the ideal weight would result in underestimation of kidney length and kidney volumes in overweight and obese patients and overestimate it in thin patients.

To answer this question, let us go back to estimation of glomerular filtration rate (GFR). The kidneys actually adjust the size to the extracellular volume (ECV), rather than the BSA [25, 26]. However, ECV correlates strongly with lean body mass [27]. As long as sex differences are accounted for [28], we can therefore use BSA based on IBW, thereby continuing with the convention of normalizing GFR to BSA. In theory, and along the lines of the paper by Marzuillo et al., kidney volume should be overestimated in thin people. To study this question, we reanalyzed the ultrasound data of 122 children (89 premature and 33 term) at age 5 years [23]. When plotting the percent difference of the kidney volume based on actual weight versus ideal weight and calculating the norms based on the artificial intelligence formula generated by Kim et al. [29] which reads 2.22 × weight (kg) + 0.252 × height (cm) + 5.138, there was a linear relationship with the BMI *z*-score (Fig. 1).

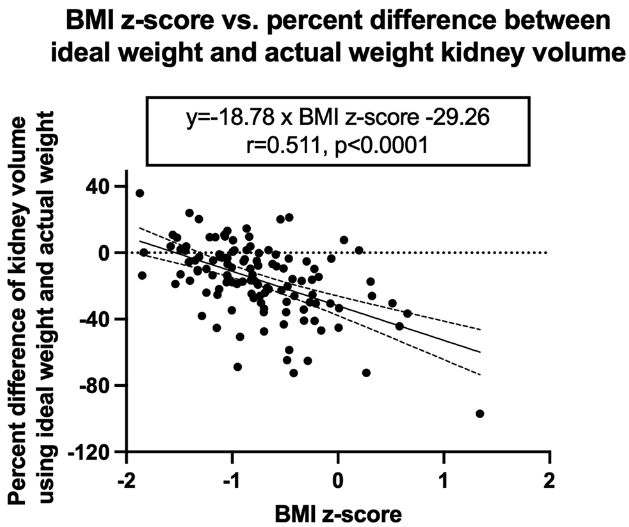

Fig. 1 The relationship between BMI *z*-score and the percentage over- or underestimation of kidney volumes based on actual versus ideal body weight calculated using the Traub method [15]. These data were from smaller Columbian children as compared to the Caucasian reference cohort [3]; therefore, the line does not cross at a BMI *z*-score at zero

Therefore, similar to eGFR, kidney volumes should not be calculated using the actual weight but rather the ideal body weight, which can be quickly determined using the Traub formula [15].

Asymmetrical acceleration of stature over time favoring the femur

As outlined above, our old BSA formulae do not cover the tall heights that we currently observe in some adolescents. Since the trunk size remains mostly preserved and the height of a person is directly proportional to the femur length [30], and in the absence of any data for tall height, we do not know anything about the accuracy of the estimation of BSA with any formula. We use the Rule of Nines to calculate burn BSA area [31]. Each anterior and posterior leg accounts for 6.5% of the BSA in children (i.e., the legs account for 26% in children), but during adolescence, it increases to 9% (i.e., the legs account for 36% in adults) [31]. Assuming a world-wide increase of height since the Du Bois BSA formula of 19–20 cm (albeit with large regional variation) [3], we can only use these formulae (even the Haycock formula) to the tallest height that was used in the most recent publication, which is not published, or approximately 175 cm for the Haycock formula [9]. It could be argued that the Mosteller and Du Bois formulae underestimate the BSA; therefore, BSA estimation by these formulae in the Ped(z) program and other formulae often provides *high* kidney volume *z*-scores without any apparent pathology.

Conclusion

At present, even though some literature suggests that indexing kidney volume rather than kidney length has a better diagnostic performance for the estimation of kidney function, we agree with Marzuillo et al. that only height-based information (or BSA based on ideal rather than actual weight, which needs to be studied) be used to assess for normal kidney length *and* volume. It is imperative that confirmation of the BSA equations or the development of new ones in large individuals takes place. The impact of the height variability of individuals from different countries in relationship to kidney volume also needs to be studied. As laudable as Obrycki's study on current kidney length and BSA among European Caucasian children is [2], we need multi-country, multi-ethnic reference intervals, similar to how the CKD-EPI formula was derived. The question is whether sitting height rather than stature can be used as reference [32]. We advocate for international collaboration to establish these reference intervals to improve the accuracy of the non-invasive ultrasound tool of kidney length and volume as a screening tool for impaired nephron endowment. Perhaps, high-resolution three-dimensional photononic scanning for data [33] and artificial intelligence for generation of a formula [29] can be used to improve BSA prediction in diverse populations.

Declarations

Conflict of interest None of the authors have any conflict of interest related to the topic of the manuscript. Dr. Maria de Ferris and Dr. Guido Filler are paid consultants to ProKidney Inc., Raleigh, NC, USA. Dr. Guido Filler is a paid consultant of Ultragenyx Canada and is on advisory boards of Horizon Pharma and Alnylam. The other authors have no paid consultancy or advisory board membership.

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