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EDITORIAL
UVODNIK

DO WE REALLY KNOW RENAL FUNCTION BEFORE ZOLEDRONATE INJECTION

DA LI ZAISTA ZNAMO FUNKCIJU BUBREGA PRE INJEKCIJE ZOLEDRONATA

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I recently attended a presentation by a bone specialist on the proposed use of intravenous zoledronate after hip fracture. I fully understand and strongly support the clinical objective of improving access to effective secondary fracture prevention in this highly vulnerable population. Intravenous zoledronate is an effective and pragmatic treatment option, and the under-treatment of patients after hip fracture remains a major clinical problem. However, I was struck by the central role given to Cockcroft–Gault creatinine clearance in the proposed renal decision pathway.

Cockcroft–Gault equation is outdated, and its historical use in drug labelling should not be conflated with physiological superiority or individual accuracy. The equation estimates creatinine clearance rather than true glomerular filtration rate (GFR); it was developed before modern IDMS-traceable creatinine assays and performs poorly against measured GFR. This has been demonstrated in a large analysis of creatinine-based equations specifically adapted to the context of drug dosage adjustment. GFR was expressed in non-indexed mL/min and validated against measured GFR in 14,804 participants. Of all equations tested - including MDRD, CKD-EPI, LMR and EKFC - Cockcroft–Gault performed worst across key metrics: bias, imprecision, P30 accuracy and correct classification into GFR categories. The authors concluded that Cockcroft–Gault should not be used for drug dosage decisions [1,2].

A further difficulty is that Cockcroft–Gault is sometimes perceived in geriatric practice as a "safer" or more conservative equation for older patients because it often gives lower values than CKD-EPI in frail or low-weight individuals. This perception is misleading. Cockcroft–Gault is mathematically driven by the term *(140 – age)* multiplied by body weight, making both age and weight major determinants of the result. In frail older patients, low body weight may markedly reduce the calculated creatinine clearance; conversely, in obese patients, use of actual body weight may produce the opposite effect. The direction and magnitude of the discrepancy are therefore not consistent. More importantly, a lower result does not imply greater proximity to measured GFR. In studies comparing creatinine-based equations with measured GFR in a drug-dosing context, Cockcroft–Gault performed worse than modern equations across key metrics, including EKFC, in terms of bias, precision, accuracy and GFR category classification [1,2].

I was also struck when a member of the audience proposed CKD-EPI equation [3] as a straightforward alternative. This is not a fully satisfactory solution, particularly in older adults. CKD-EPI is known to overestimate GFR in older individuals, whereas the EKFC equation [4], - specifically developed and validated in Europe - was designed to improve age modelling and reduce age-related bias across the full age spectrum. EKFC is now recommended by the European Federation of Clinical Chemistry and Laboratory Medicine for use in European laboratories [5,6]. However, EKFC should not be applied uncritically for drug dosing decisions [7]. For drug dosage adjustment, the clinically relevant quantity is not GFR normalised to 1.73 m^2, but the patient's absolute excretory kidney function, expressed in mL/min. Drug clearance depends on the individual patient's absolute filtration capacity, not on the value that would be obtained if their body surface area were 1.73 m^2. Accordingly, when CKD-EPI, EKFC or any indexed eGFR equation is used for drug-dosing purposes, the result should be de-indexed according to body surface area. This point is especially important in frail older

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patients following hip fracture, who frequently have low body weight and low body surface area [2].

Even this, however, does not fully resolve the problem. All creatinine-based equations remain estimates. Their standard performance metric – the P30 – defines an estimate as accurate if it falls within ±30% of measured GFR. Around a decision threshold of 30 mL/min, this level of uncertainty is clinically substantial: a measured GFR of 30 mL/min may correspond to an estimated value between 21 and 39 mL/min and still be considered "accurate". For Cockcroft–Gault, the problem is even more pronounced still: among patients with a measured GFR of 30–45 mL/min, the P30 is only 63.5%; among those with a measured GFR of 15–30 mL/min, it falls to 49.5% [2]. In other words, precisely within the range where renal thresholds for zoledronate become clinically relevant, Cockcroft–Gault provides a highly uncertain estimate.

This is not merely a statistical concern. Frail older patients following hip fracture are precisely those in whom creatinine-based estimation is most unreliable: sarcopenia, acute illness, perioperative changes, hydration status, diuretic use and non-steady-state creatinine can all undermine the validity of any equation. A patient calculated at 32 mL/min by Cockcroft–Gault, CKD-EPI or even de-indexed EKFC may have a true measured GFR that is substantially lower or higher. A value in the region of 30–35 mL/min should therefore be interpreted as a zone of uncertainty, not as a reliable individual measure of renal function [8].

This concern is particularly relevant when the drug in question is potentially nephrotoxic, or when the clinical decision hinges on a narrow renal threshold. The importance of measured GFR has already been emphasised in the context of drugs such as cisplatin, but the principle is broader: when the consequences of misclassification are clinically significant, reliance on creatinine-based estimation may be insufficient [2].

In this setting, arbitrating between Cockcroft–Gault, CKD-EPI and EKFC when a patient is close to the renal threshold is not a productive approach. Cockcroft–Gault is outdated and poorly performing; CKD-EPI is problematic in both younger and older adults; EKFC is a more appropriate modern European estimate, but for drug dosing, it must be de-indexed and, even then, remains an estimate rather than a measurement. If renal function is truly central to the decision to administer intravenous zoledronate, the scientifically robust approach is to measure GFR directly.

In my view, plasma iohexol clearance is the most appropriate solution. It provides a true measured GFR, is feasible in routine clinical laboratory practice, and avoids the false precision of creatinine-based equations. This is not an exotic or poorly standardised approach. The European Kidney Function Consortium has recently published a consensus paper in *Kidney International* dedicated to the standardisation of plasma iohexol clearance measurement in adults, covering patient preparation, iohexol administration and safety, blood sampling strategies, laboratory analysis, GFR calculation and implementation procedures [9]. Furthermore, iohexol measurement can be embedded in a laboratory quality assurance framework: laboratories performing iohexol assays may participate in external quality assessment schemes, which is essential for reproducibility and inter-laboratory comparability [10].

This approach is consistent with European laboratory recommendations. The EFLM recommendations based on KDIGO 2024 address iohexol plasma clearance standardisation and support broader implementation of appropriate GFR assessment strategies across European laboratories [5]. In this context, measured GFR by plasma iohexol clearance should not be regarded as a luxury, but as the appropriate test when a binary treatment decision depends on a narrow renal threshold in a frail older patient.

The central question is therefore not whether the cut-off should be 30 or 35 mL/min, nor whether Cockcroft–Gault should be replaced by CKD-EPI. The real issue is whether it is acceptable to base a binary safety decision in frail older patients on an imprecise creatinine-based estimate. When the degree of uncertainty is large, and the consequences of misclassification are clinically relevant, measured GFR by standardised plasma iohexol clearance, performed within a quality-controlled laboratory framework, is not a luxury; it is the appropriate test.

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