Bioanalytical Aspects and other non-GFR considerations in deciding on the Formula To use in GFR Assessment in Pediatric Patients

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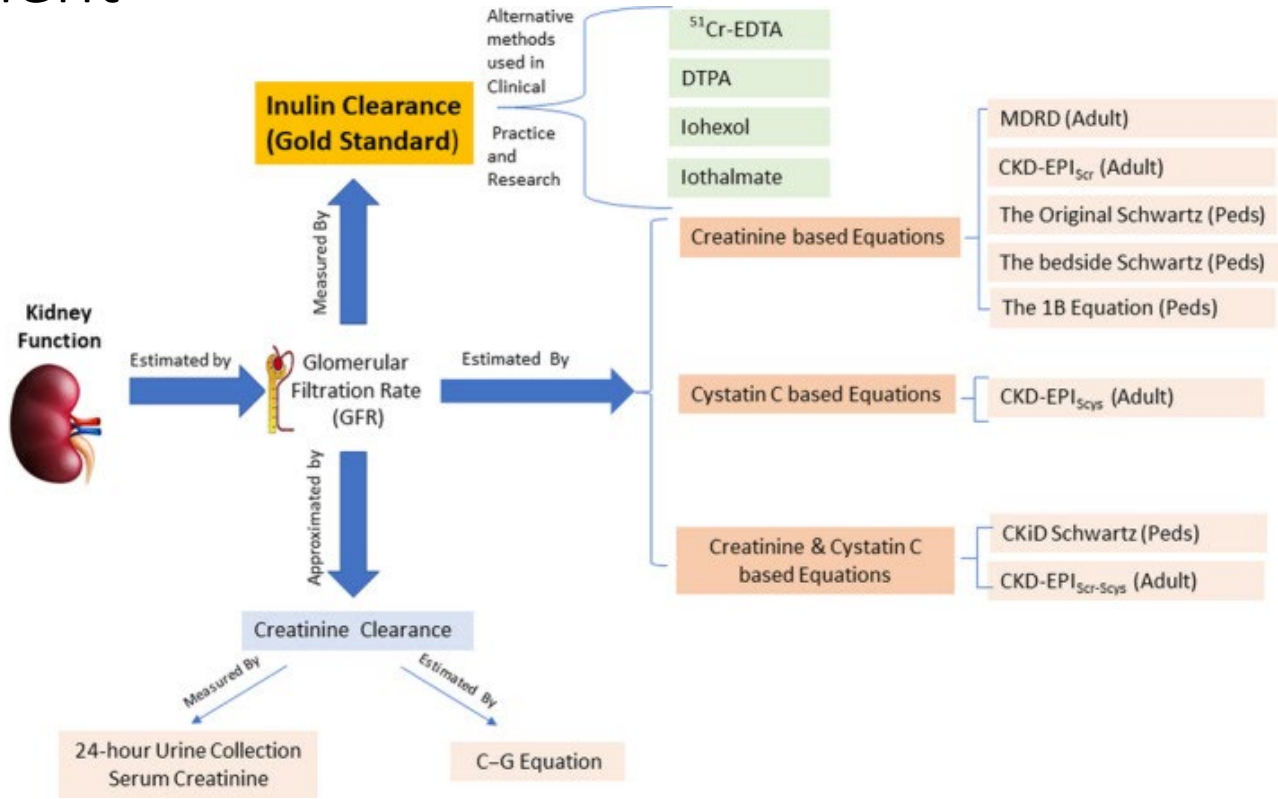
Conflict of Interest

- Ash Sharma is an employee of Boehringer Ingelheim Pharma Inc., USA.
- Concepts presented here reflect the opinion of Ashish Sharma and not necessarily endorsed by his employer.
- Some of the concepts presented here were discussed and developed as a part of the IQ consortium group on organ impairment and published*.

*Sharma et al., Clin Pharmacol Ther 2022:112(5):946-958

Markers and Equation for Renal Function Assessment



Analytical methods to measure creatinine

Jaffe method (Rehberg 1926)

- Creatinine+Folic acid – yellow orange color – Photometric measurement.
- Reaction unspecific (protein, glucose, ascorbic acid, ketone bodies, pyruvate, guanidine, cephalosporins, aminoglycosides and bilirubin) – issue in diabetics, cirrhosis, etc.

Enzymatic method

- Enzymatic reactions with creatinine – red dye – photometric measurement
- Interferences reduced (e.g., ketone bodies, ascorbic acid)
- **Performs better than Jaffe in conditions such as diabetes, cirrhosis**

IDMS standardization

- Concern about interlaboratory variability due to different internal standard
- National Institute for Standards and Technology (NIST) released a standard reference material (SRM 967a-Creatinine in Frozen Human Serum)
- SRM 967a traceable to IDMS reference measurement procedure. Used for establishing calibrations for routine creatinine measurement procedures
- Creatinine bioanalytical method traceable to IDMS reference called IDMS traceable method
- Output between IDMS traceable and IDMS non traceable methodology can vary from 10% to 20% depending on the reference material used by individual laboratories
- Newer GFR equations are established and intended to be used ONLY with IDMS traceable creatinine measurements

Adult equations – IDMS Traceable creatinine Analysis vs Not

Equation	IDMS Standardized Assay ?
Cockcroft-Gault	No
“Original” MDRD	No
Modified MDRD	Yes
$CKD\text{-}EPI_{Scr}$ (+ Refit for Race)	Yes
$CKD\text{-}EPI_{Scr\text{-}Scys}$ (+ Refit for Race)	Yes
Japanese 3 variable equation	Yes

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Pediatric Equations – IDMS standardized creatinine equations or Not ?

Equation	IDMS Standardized Assay ?
Creatinine based “Original” Schwartz	No
Creatinine based “Bedside” Schwartz” (2009)	Yes
Cystatin C based equation (2012)	NA
Creatinine-Cystatin C based CKID (2012) “1B equation”	Yes Yes

The cystatin C values are not corrected for IFCC calibration. IFCC calibrated values should be divided by 1.17 before entered as input. (Schwartz et al. Pediatr Nephrol 35:279-285, 2020).

Pediatric GFR Calculator | National Kidney Foundation

Should Pharma Industry still utilize the Cockroft-Gault formula or original Schwartz formula ?

- Majority of labs have switched their bioanalytical assay to IDMS standardized serum creatinine assay
- Cockroft-Gault formula and the original Schwartz formula were designed using non-standardized serum creatinine assay and use of IDMS-standardized creatinine output can result in up to 20% overestimation of renal function.
- Additionally, Cockroft-Gault equation was built using data from 249 White men and hence the equation doesn't predict renal function as accurately for other populations. Equation has body weight (not linked to muscle mass/nephrons) – biased output for individuals with high or low BMI. This equation is not validated for use in children (ref - use in adolescents).
- The US National Kidney Foundation and global KDIGO guidelines recommend altenatives (Height/Serum creatinine shown best correltion with iohexol GFR).

Thoughts on the Creatinine Based Formulas

- Consider whether labs are utilizing non-IDMS standardized serum creatinine assays in making lab decisions.
- Important to be aware if non-IDMS standardized Jaffe reaction was used in quantifying serum creatinine in one of the local labs in a multinational clinical trial (CRF).
- If non-IDMS standardized assay was used in a site/lab, it could be more appropriate to use an alternate formula

Need to be cautious when interpreting results:

- If the drug being developed is an OCT2/MATE inhibitor or if patients in the clinical trial are on a drug that inhibits either transporter.
- Cystatin based formula can be used to assess renal function instead of creatinine where drug inhibits serum creatinine excretion

Impact of diet and exercise on serum creatinine levels

- Exercise

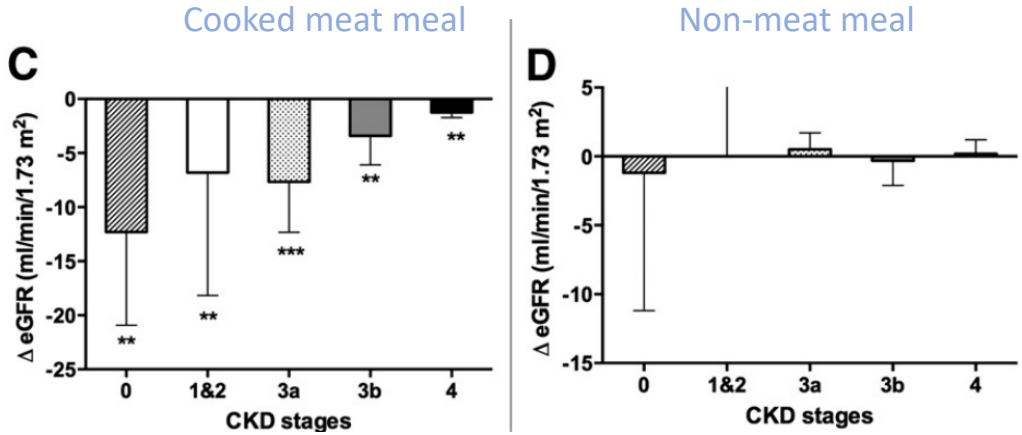
1.) Approx. 40% increase in serum creatinine (20% increase in cystatin c) following marathon.

2.) Higher influence on amateurs and untrained individuals.

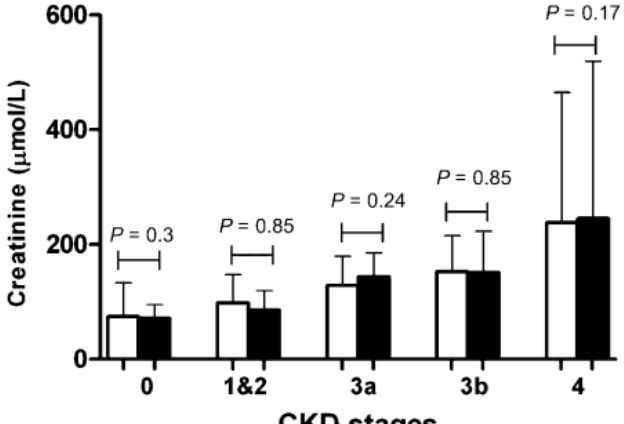
3.) Study participants should abstain from rigorous exercise 24 hours prior to sampling for serum creatinine/cystatin c.

Food: Changes in Serum creatinine 2h after cooked meat or nonmeat meal

- Consumption of cooked meat before Sampling for serum creatinine leads to underestimation of GFR



- A 12 hours gap between consumption of cooked meat and sampling of creatinine is ideal to avoid confounding factors.



Factors that influence Serum Markers for eGFR

- **Serum Creatinine**
- Meat consumption
- Exercise
- Medications (e.g., Bacitracin, cimetidine, Cephalosporins, fenofibrate, etc)
- Race
- Cystic fibrosis
- Kidney transplantation
- Pregnancy

Serum Cystatin

- Obesity
- Thyroid disorders
- Viral load in HIV patients
- Cancer
- High dose steroid therapy
- Inflammation
- Smoking

Further Points

- Clearly indicate during drug label development, which GFR equation was used during drug development. Remove the guessing game for drug prescribers and dispensers!
- Where possible, stay consistent in the drug development program with respect to equation.
- Alternate formula to adjust the dose of a conmed in a clinical trial may be necessary.