

Cystatin C: A New Standard to Measure GFR?



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Objectives

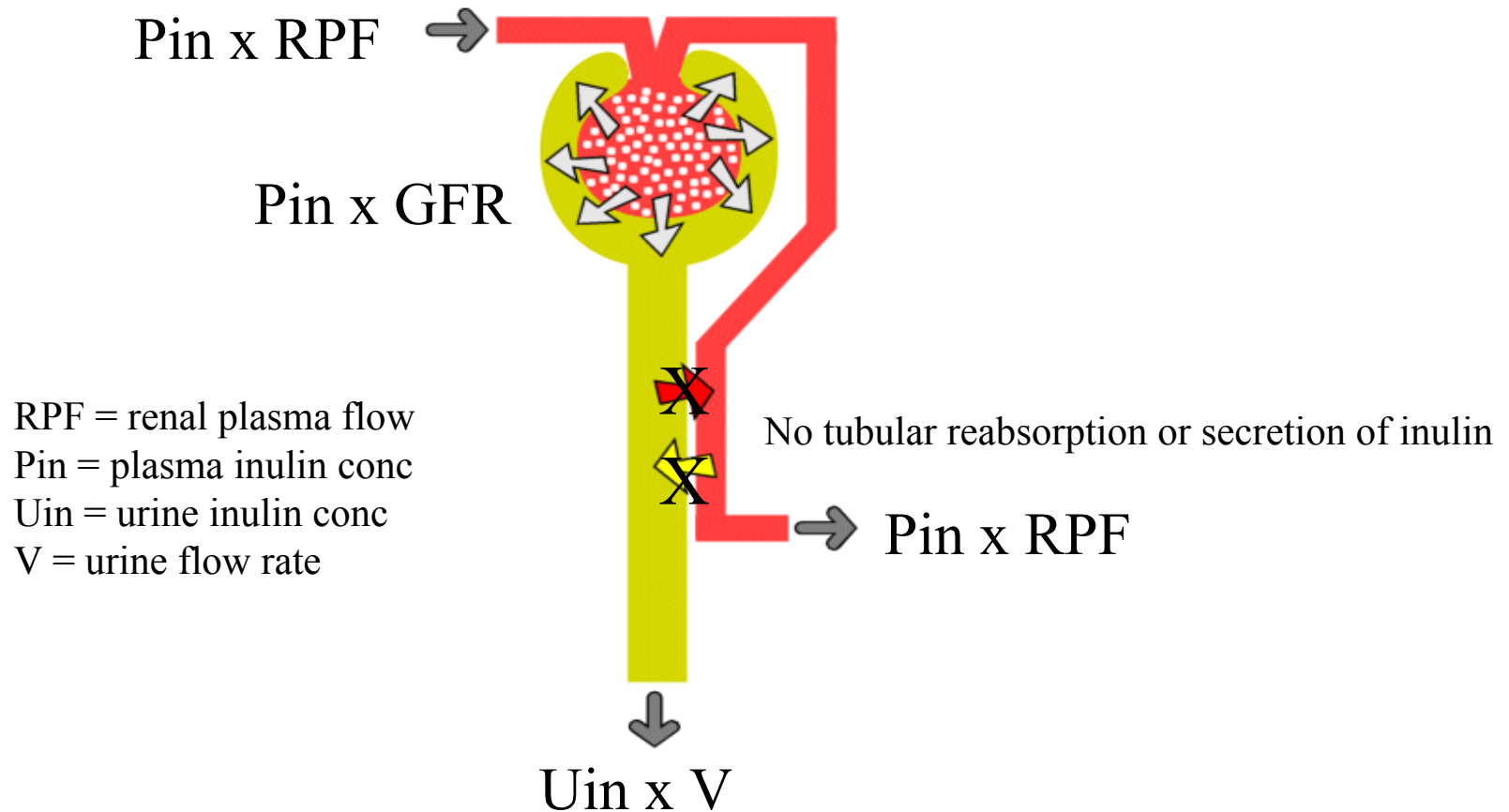
- Review measurement of GFR
- Discuss current standards for estimation of GFR and their limitations
- Introduce cystatin C and show why it is widely studied as a filtration marker
- Compare cystatin C performance to serum creatinine to estimate GFR
- Highlight use of cystatin C in specific clinical scenarios



Measurement of GFR

- Impossible to measure directly
- Can be estimated by a marker that is filtered but not secreted, reabsorbed, synthesized, nor metabolized by kidney
- Gold standard is inulin clearance

Measurement of GFR



$$\begin{aligned} \text{Amount Filtered} &= \text{Amount Excreted} \\ P_{in} \times GFR &= U_{in} \times V \end{aligned}$$



Limitations of inulin

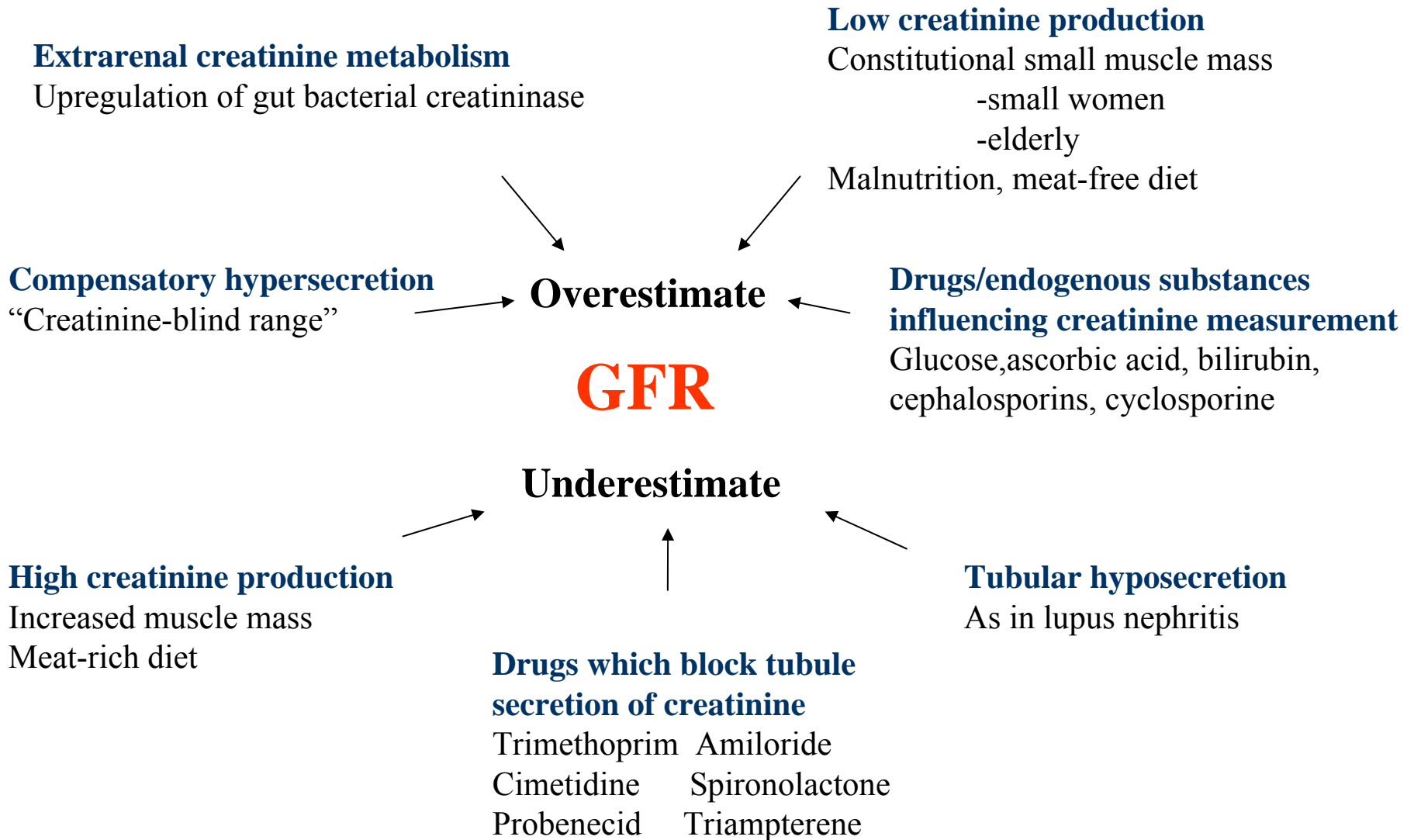
- Cumbersome to measure
- Exogenous and expensive
- Other exogenous markers (iohexol, iothalamate, radiolabeled DTPA or EDTA) with similar limitations



Creatinine as a measure of GFR

- Derived from creatine metabolism in skeletal muscle and released into circulation at a relatively constant rate
- Freely filtered, neither metabolized nor reabsorbed
- $GFR \times SCr = \text{constant}$ (SCr production)
- Inexpensive to measure (25¢)

Creatinine induced misinterpretation of GFR

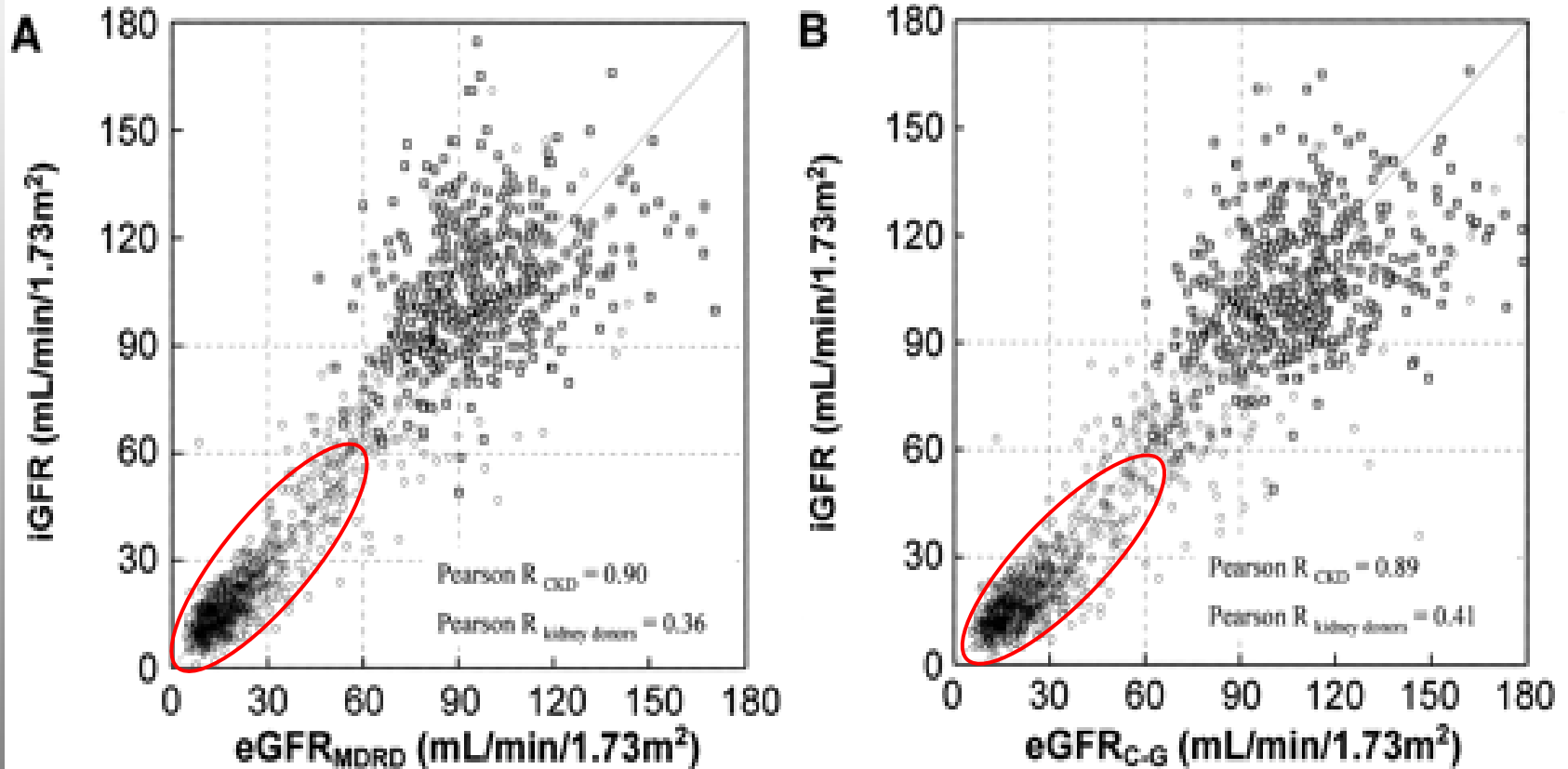




Creatinine based equations to estimate GFR

- Attempt to control for variables that affect creatinine levels
- Cockcroft-Gault (1976): age, lean body weight
- MDRD (1999): age, gender, race, BUN, Albumin
- Each equation also incorporates serum creatinine value

Performance of creatinine-based equations to estimate GFR







Introduction to cystatin C

- Member of the cystatin family, a group of cysteine protease inhibitors
- Only member produced by all human nucleated cells
- Rate of production is constant
- Low-molecular weight protein



Introduction to cystatin C

- Freely filtered at glomerulus
- Not secreted
- Reabsorbed but completely catabolized by proximal tubular cells
- Independent of muscle mass, age, sex
- No known mechanism of non-renal clearance



Cystatin C versus creatinine in patients with native kidney disease

- Since 1985, 29 studies performed
- Measured GFR using gold-standard method (inulin, radiolabeled isotope scan, etc.)
- Correlation of reciprocal of cystatin C and creatinine compared to measured GFR
- Based on precision and accuracy, cystatin C was found to be superior in 17 studies with 12 studies showing no significant difference
- **NO STUDY SHOWED SUPERIORITY OF CREATININE OVER CYSTATIN C**



Cystatin C versus creatinine in kidney transplant patients

- Since 1998, 14 studies performed
- Similar measurement of GFR and comparison of reciprocal values of cystatin C and creatinine
- Superiority of cystatin C found in 10 studies with 3 studies showing no significant difference
- One study displayed superiority of creatinine



Cystatin C in dialysis patients

- Hoek, et al devised a cystatin C-based formula to calculate residual GFR
- This formula compared favorably to MDRD equation in determining rGFR
- Formula was derived in the same population in which it was tested
- No data showing the usefulness of cystatin C to assess adequacy of each dialysis session



Controversy surrounding cystatin C

- Methodological flaws in studies that show superiority (small sample size, different cutoffs of GFR to define disease, assay variations)
- Production well known to be altered in hypo- and hyperthyroid states as well as with administration of high dose steroids



Controversy surrounding cystatin C

- Isolated studies report age, gender, weight, height, cigarette smoking, and C-reactive protein levels may affect cystatin C production or catabolism
- One study reports potential extra-renal elimination of cystatin C
- Increased cost of measurement versus serum creatinine (\$3 vs 25¢)



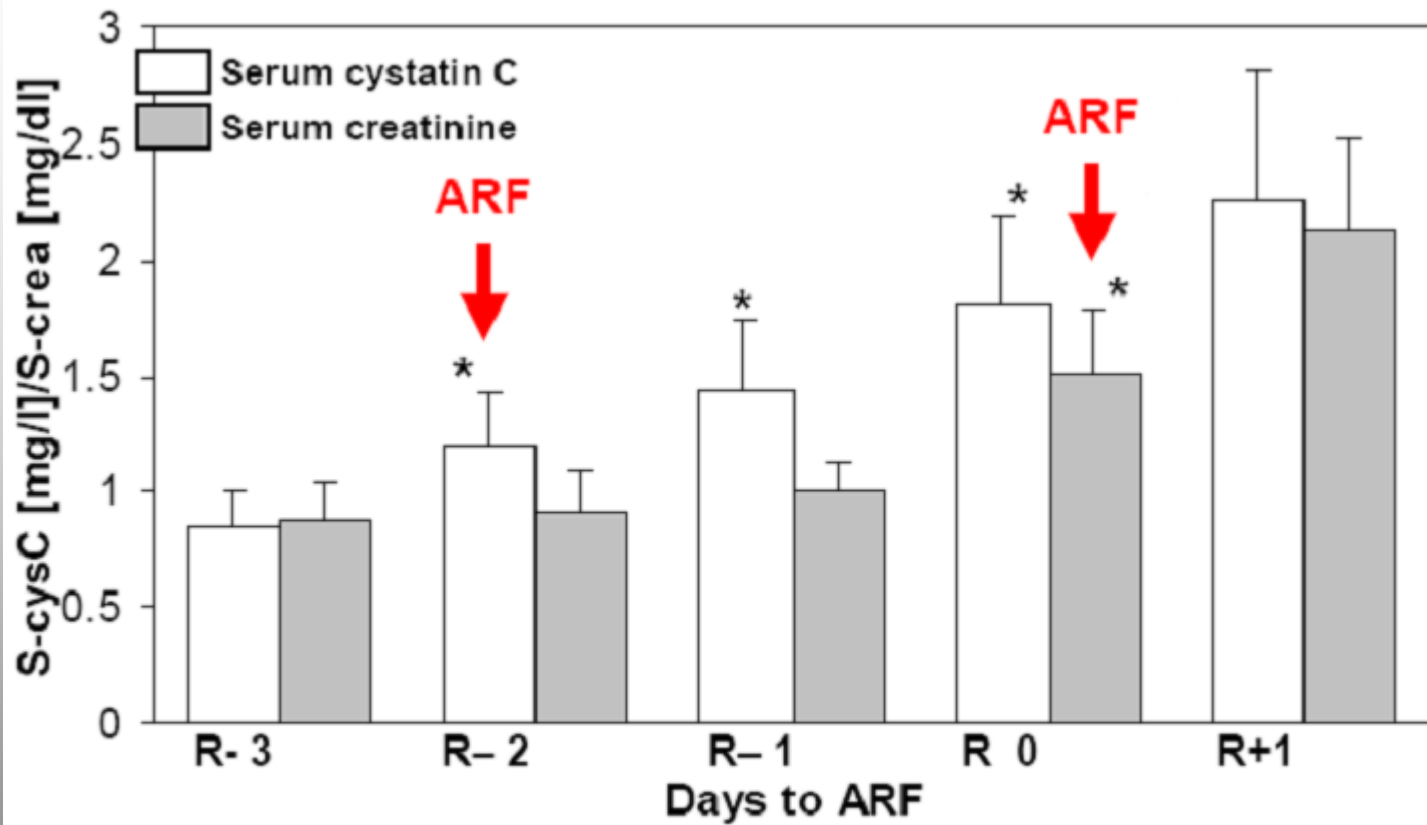
SPIRITUALITY

EVEN IN THE UNLIKELY EVENT THAT GOD DOES CARE ABOUT BASEBALL,
IT'S PRETTY OBVIOUS HE DOESN'T GIVE A RAT'S ASS ABOUT THE CUBS.



Use of cystatin C to detect early renal failure

- 85 ICU patients with normal baseline GFR determined to be at high risk for renal failure based on age, DM, development of shock
- Daily measurements of cystatin C and creatinine
- Acute renal failure defined as increase in baseline serum marker of $\geq 50\%$
- 44 patients developed renal failure; the other 41 patients served as controls

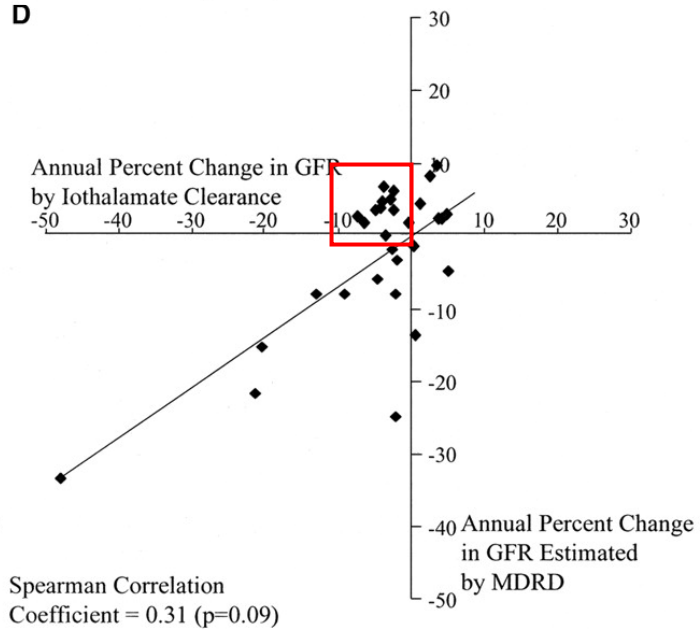
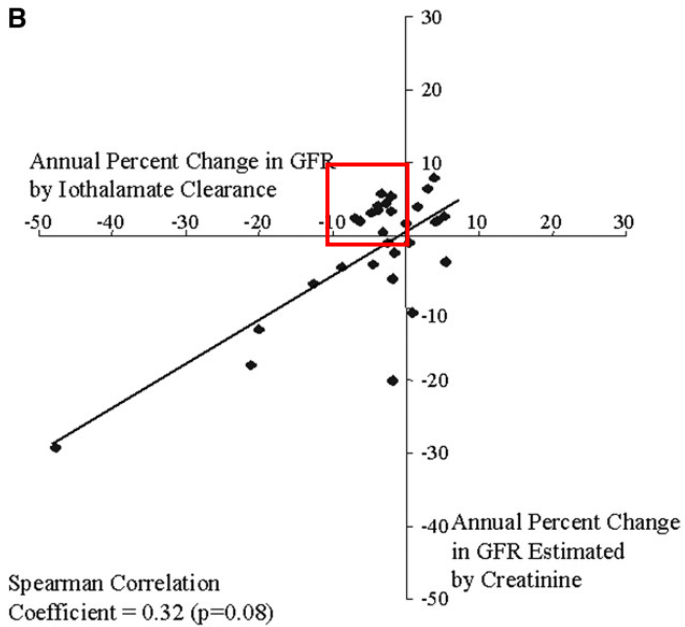
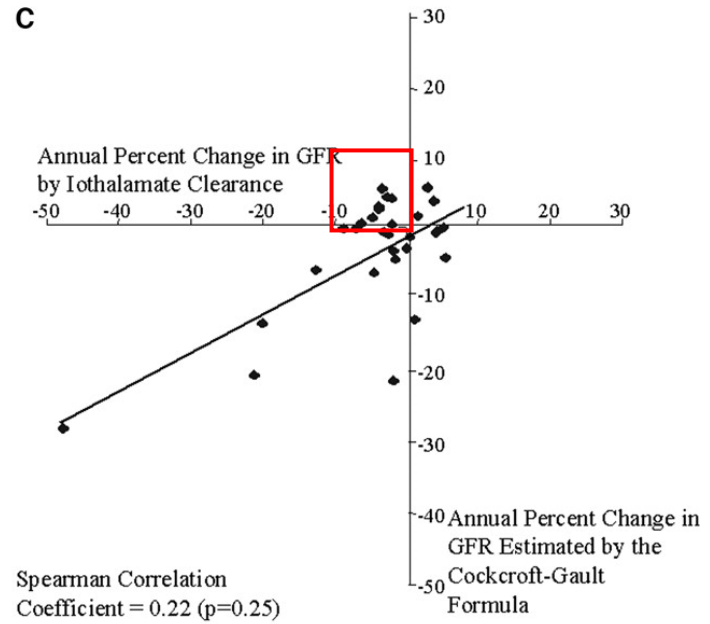
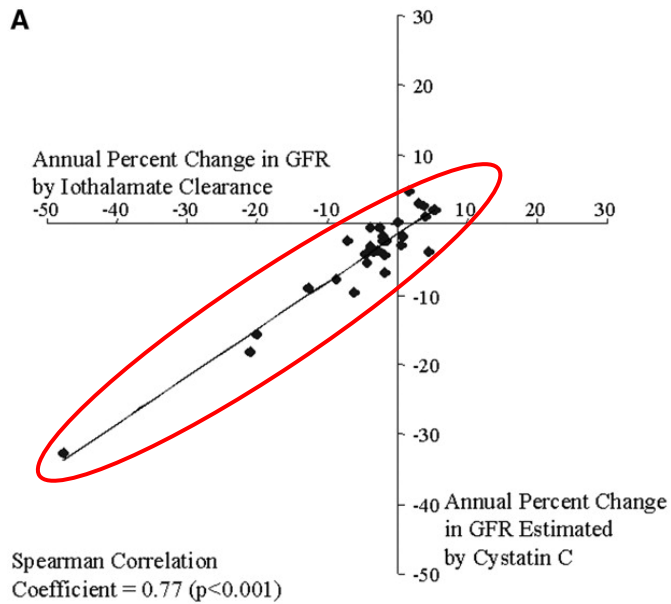


*Clinically significant ARF as determined by increase of baseline serum marker of $\geq 50\%$

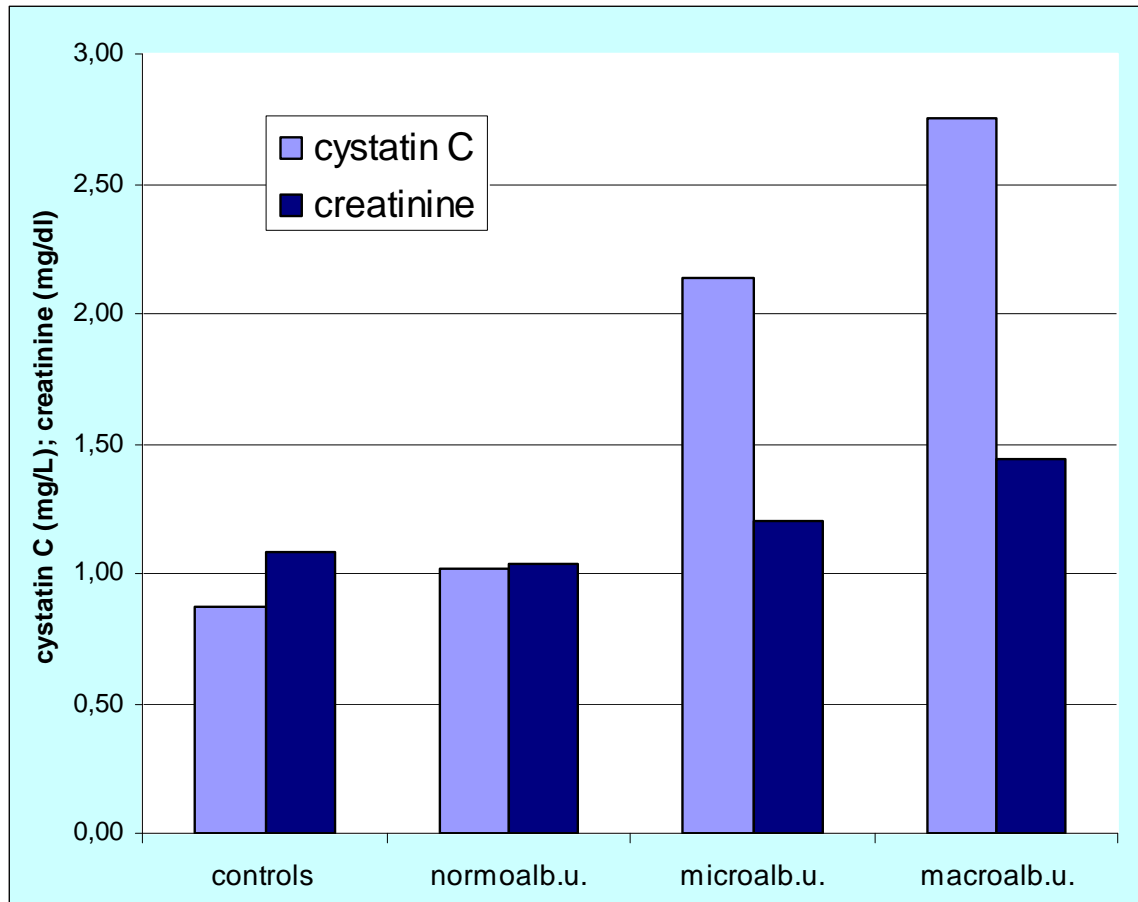


Use of cystatin C to detect early decline in GFR in diabetics

- Population of diabetics with a baseline GFR ≥ 120 ml/min/1.73m² as defined by iothalamate clearance
- Patients followed for 4 years
- Yearly cystatin C and creatinine levels drawn; iothalamate clearance also repeated yearly



In Type II Diabetes



Piowar et al, Arch Immunol Therap Exp. 1999; 47: 327-331



Summary – Take Home Points

- Serum creatinine as a surrogate of GFR has many limitations
- Cystatin C fulfills many characteristics of an ideal filtration marker
- Studies evaluating ability of cystatin C and creatinine to estimate GFR have trended towards superiority of cystatin C



Summary – Take Home Points

- Cystatin C may be particularly useful in specific patient populations that fall in the “creatinine-blind range”
- Further work must be done to fully evaluate potential limitations of cystatin C before it is ready to supplant creatinine as the most widely used filtration marker