



Disclosure of Financial Relationships

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Nephrologist's Perspective

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Clinical markers (creatinine based eGFR and spot urine albumin/creatinine) are good enough for what we can now do therapeutically in diabetic and hypertensive CKD.

Needs

- Predictive markers for:

Prognostication for rate of progression

Disabilities e.g. neurocognitive deficits

Mechanism and drug targets

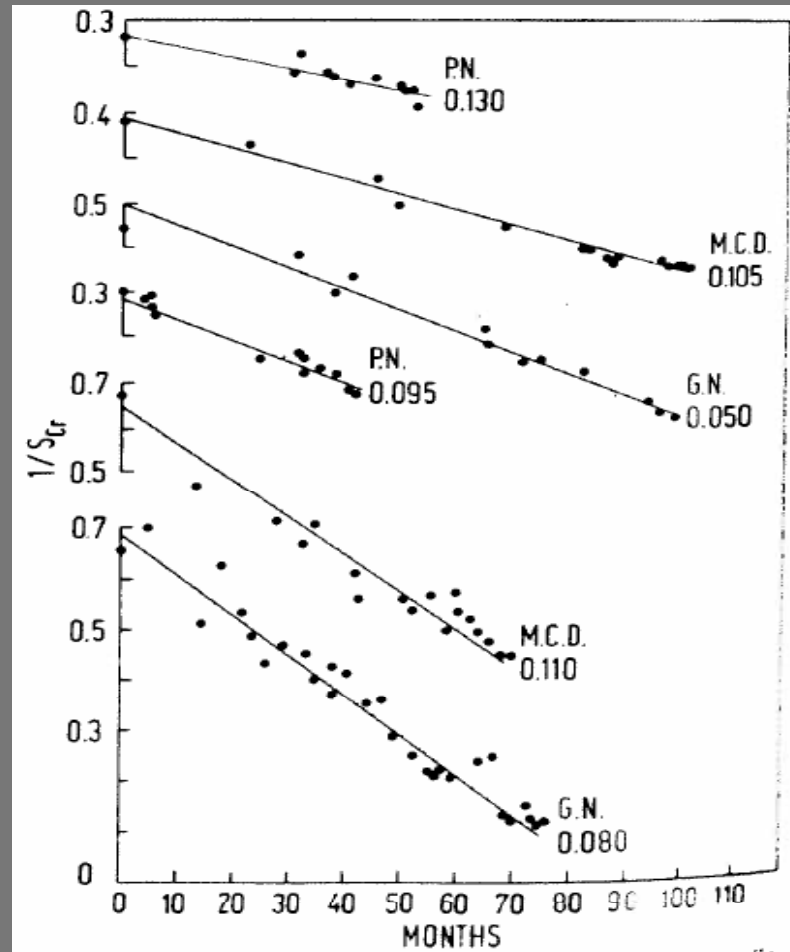
Stratification for small trials

- Surrogates for larger trials

Approaches to Diagnosing and Monitoring Chronic Kidney Disease

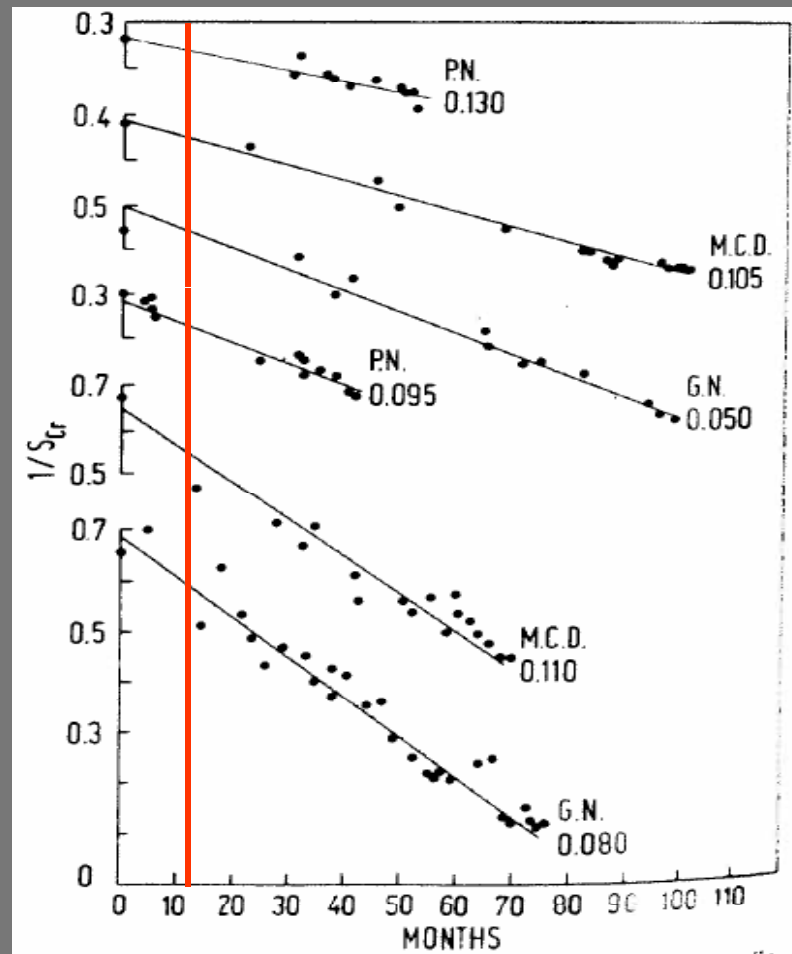
- Clearance
- Synthesis
- Glomerular Permeability / Proteinuria
- Markers of Cellular Injury

GFR Decline Is Linear and Predictable



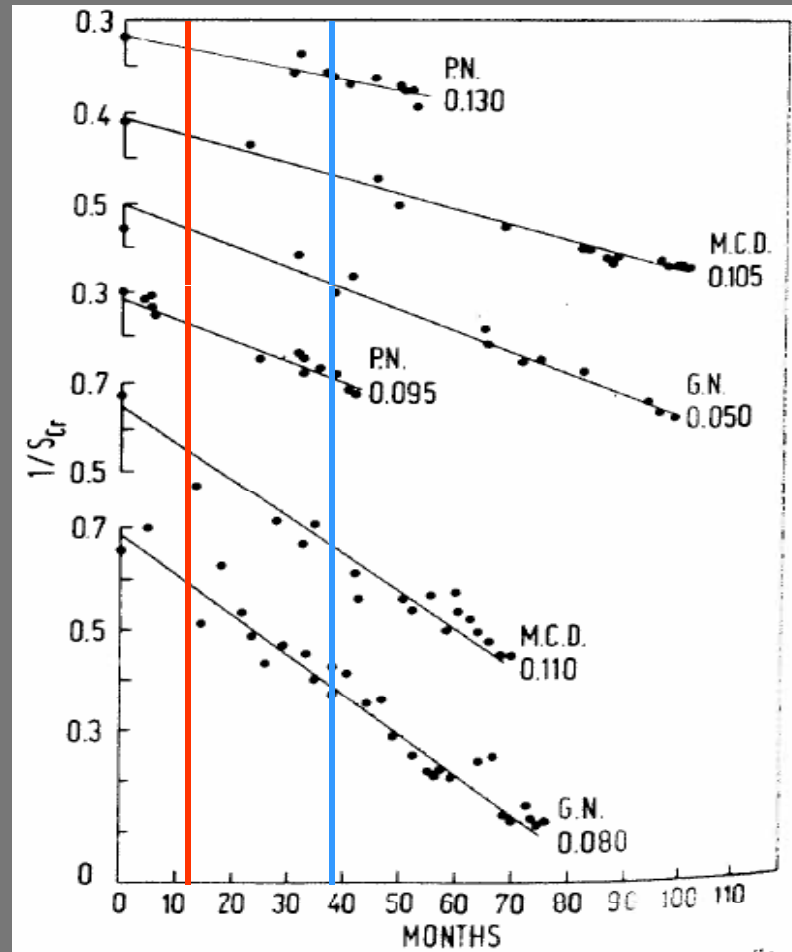
Mitch et al, 1976

GFR Decline Is Linear and Predictable



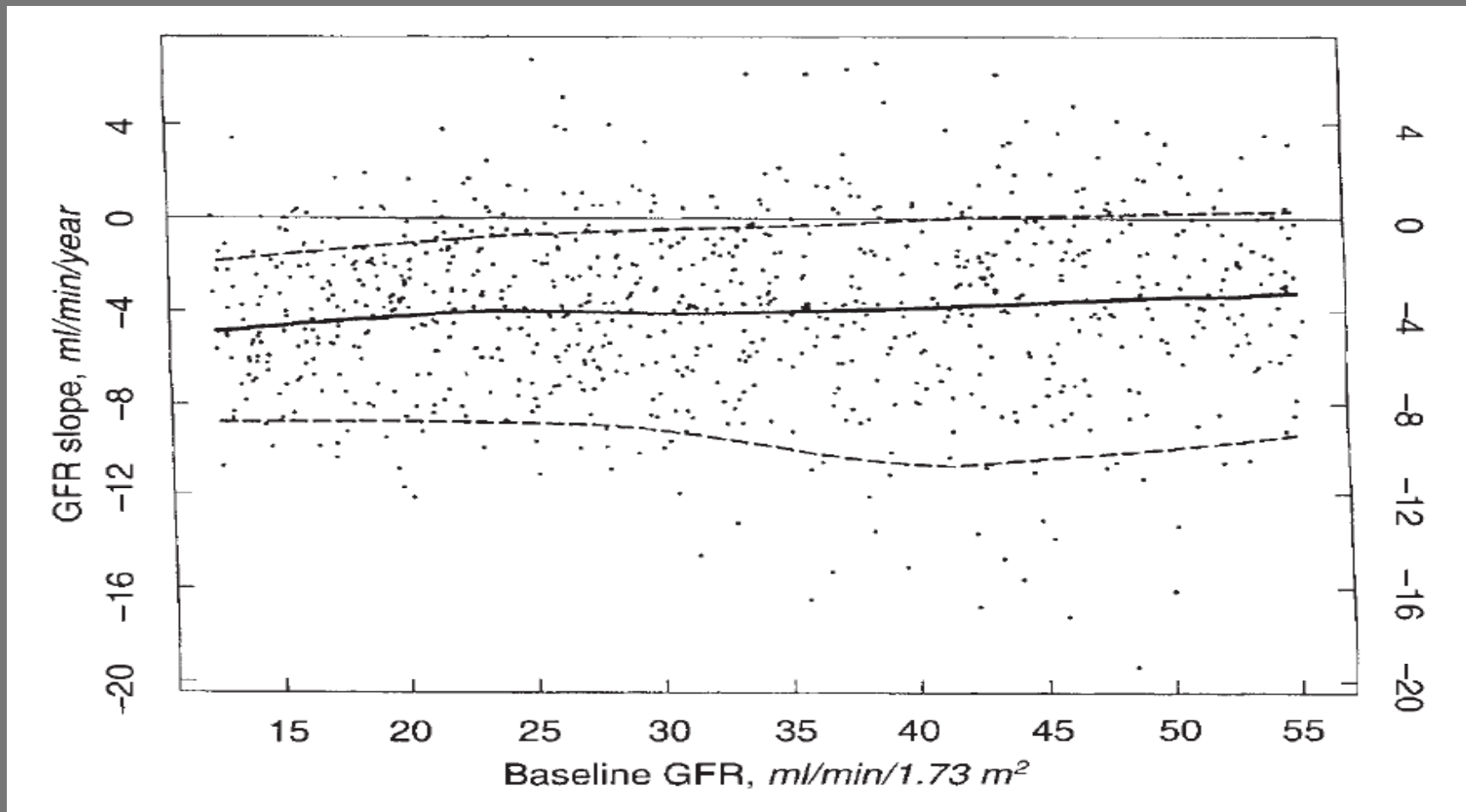
Mitch et al, 1976

GFR Decline Is Linear and Predictable With Enough Points and Time to Establish a Trend



Mitch et al, 1976

GFR Itself Does Not Predict Progression Rate



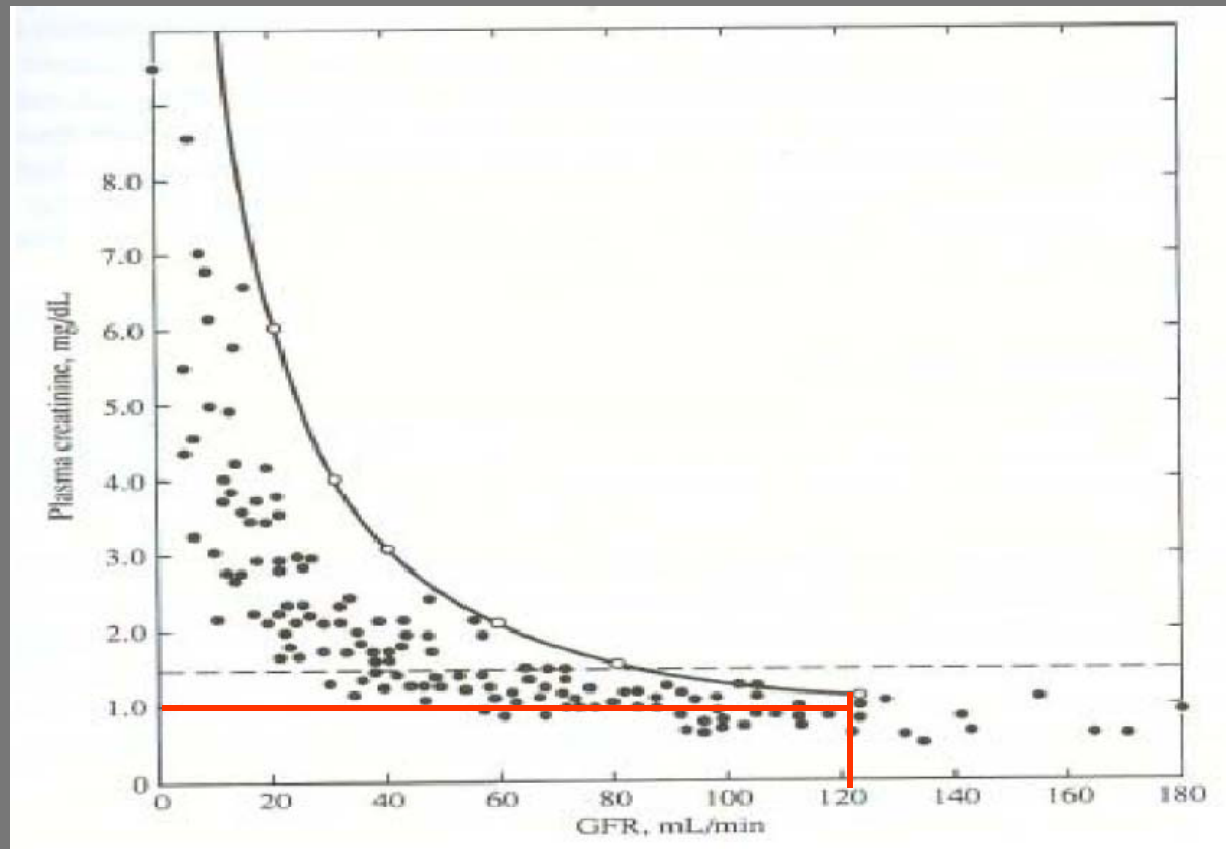
Hunsicker et al, 1997

Clearance Based Approaches Will Always Face the Problem of an Inverse Relation

$$\begin{aligned} \text{Clearance} &= \frac{\text{Removal}}{\text{Plasma Concentration}} \\ &= \frac{\sim\text{Constant}}{\text{Plasma Concentration}} \end{aligned}$$

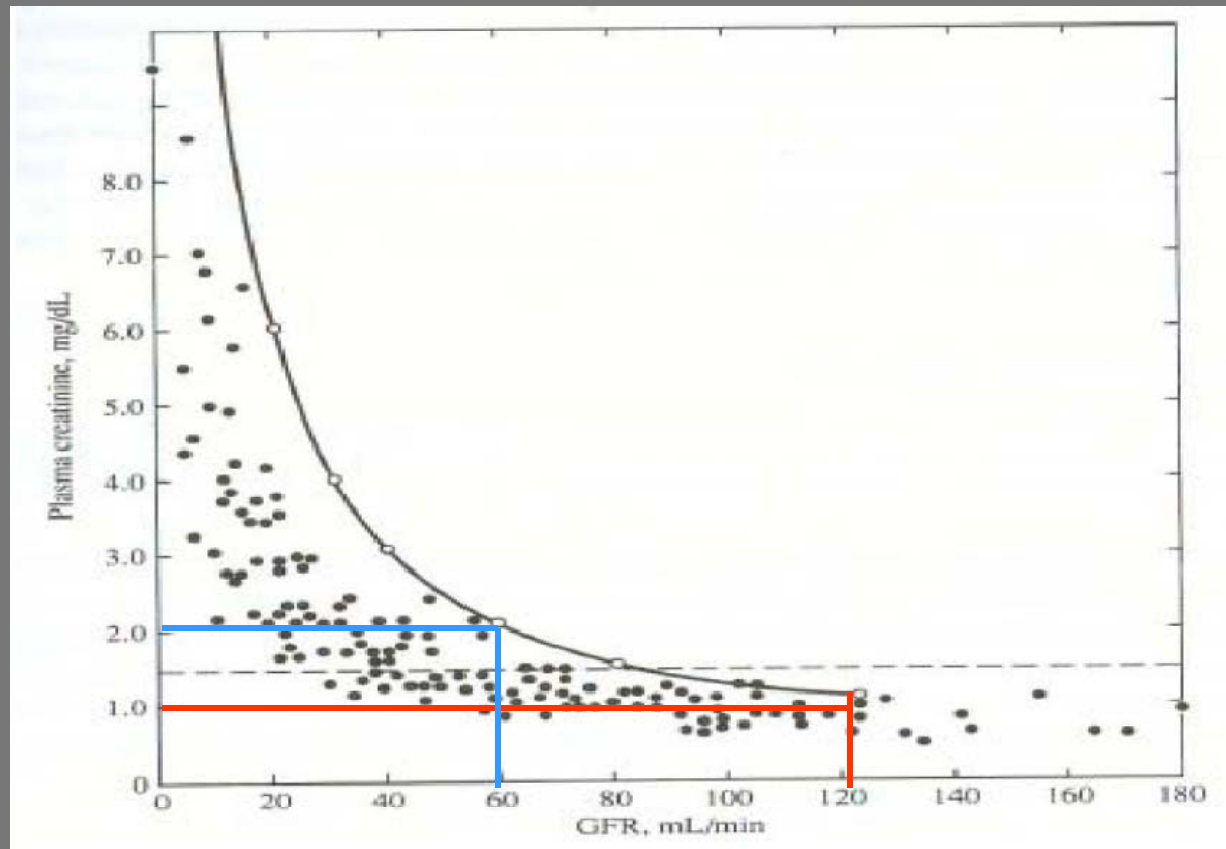
$$f(X) = \frac{1}{X}$$

An Inverse Relation Means the Earliest Changes in Clearance Will Have the Smallest Effects on Plasma Levels



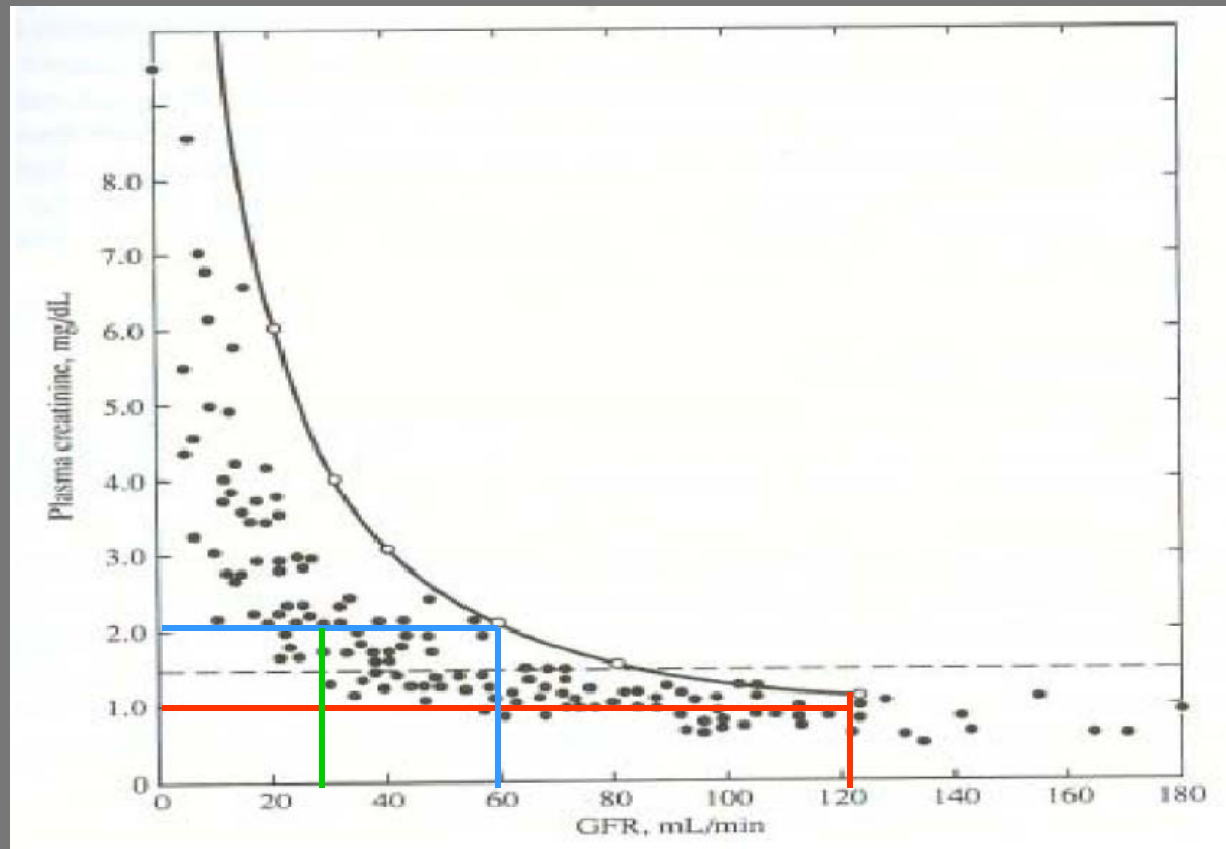
Shemesh et al, 1985

An Inverse Relation Means the Earliest Changes in Clearance Will Have the Smallest Effects on Plasma Levels



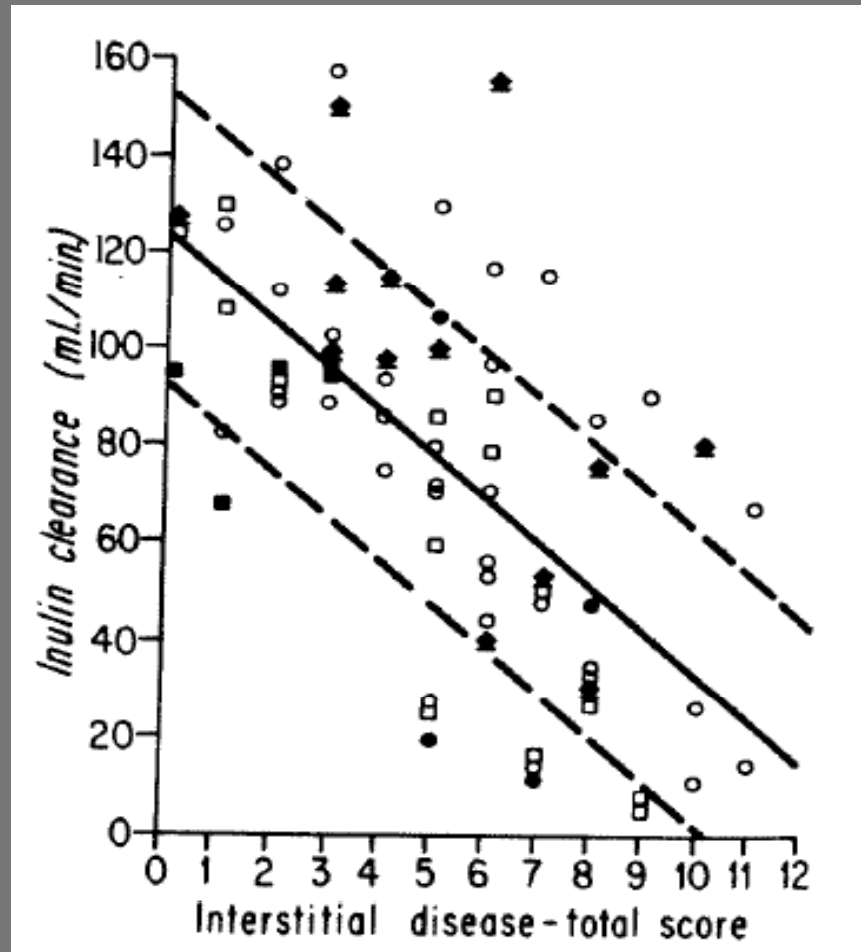
Shemesh et al, 1985

An Inverse Relation Means the Earliest Changes in Clearance Will Have the Smallest Effects on Plasma Levels **But Worse for Creatinine**



Shemesh et al, 1985

TID Correlates with GFR



Schainuck et al, 1970

Decreased Renal Organic Anion Secretion and Plasma Accumulation of Endogenous Organic Anions in *OAT1* Knock-out Mice*

Received for publication, July 22, 2005, and in revised form, October 20, 2005. Published, JBC Papers in Press, December 14, 2005, DOI 10.1074/jbc.M508050200

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Organic anion	Plasma			
	WT		KO	
	Mean	S.E.	Mean	S.E.
			μM	
3-Hydroxyisobutyrate	0.00	0.00	293.54	64.69
3-Hydroxybutyrate	0.00	0.00	481.61	141.15
4-Hydroxyphenyllactate	4.33	0.53	11.76	2.24
Benzoate	0.00	0.00	16.91	6.86
2-Hydroxy-3-methylvalerate	8.45	2.41	28.62	8.55
3-Hydroxypropionate	0.00	0.00	12.68	5.60
<i>N</i> -Acetylaspartate	5.46	4.52	19.93	5.19

Summary (1)

- Clearance has the virtue of measuring a function of the kidney
- Clearance has the deficit of small changes in plasma levels with early disease
- Clearance of GFR markers does not predict subsequent rates of decay
- Doubling serum creatinine is more than halving of GFR and pushes studies to advanced CKD
- Secretory markers have been little explored

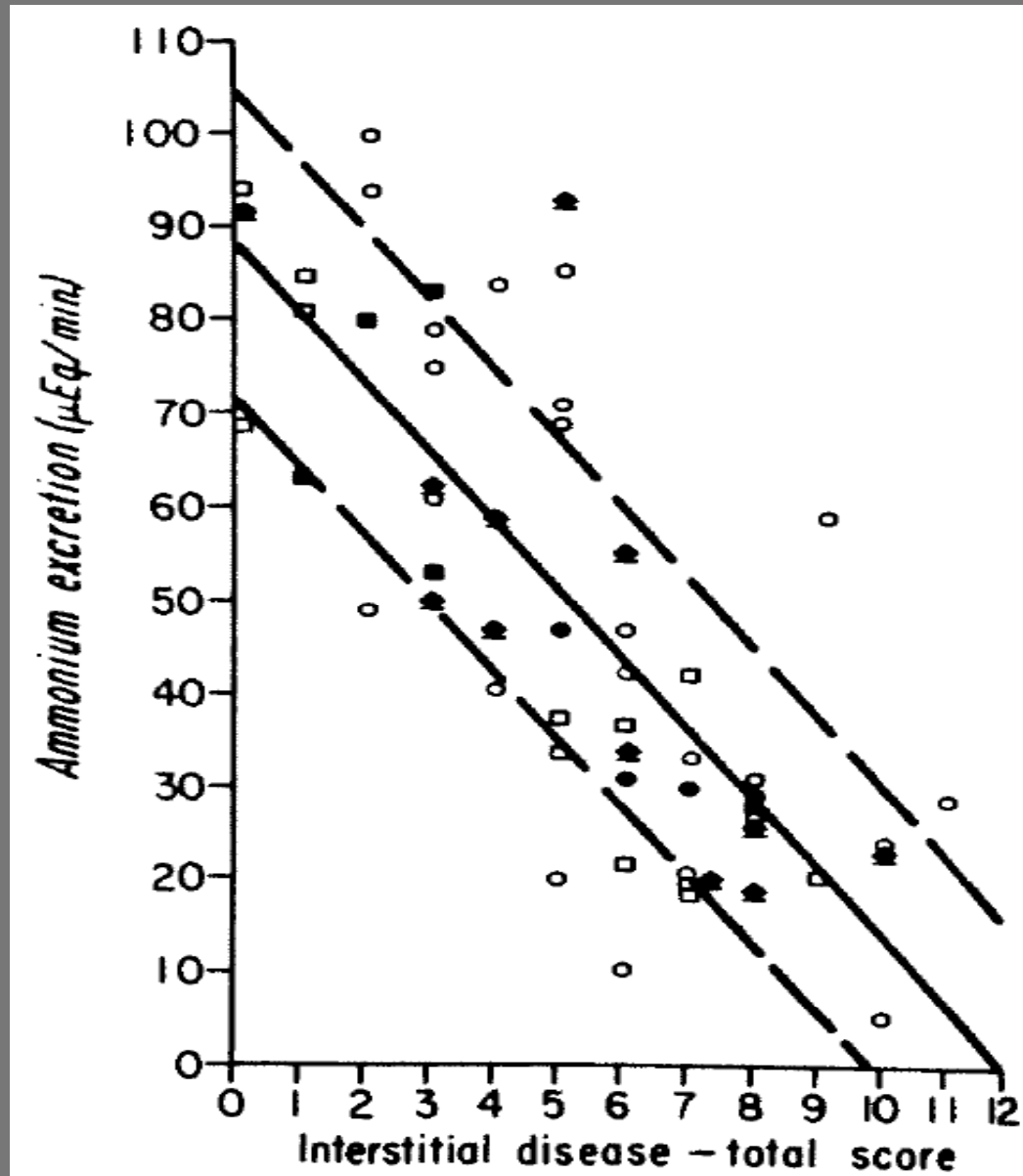
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Synthetic Functions of the Tubule

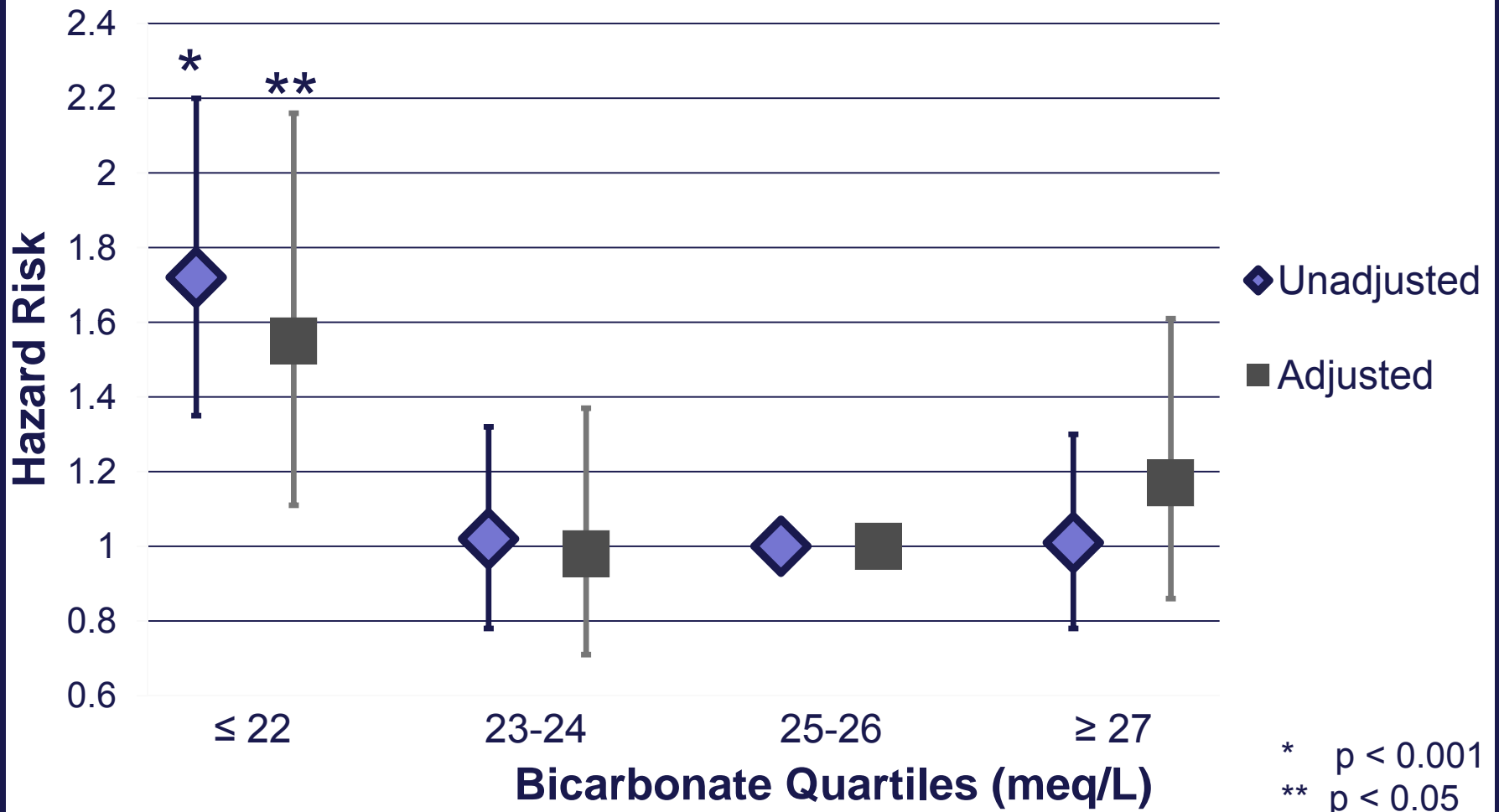
- Erythropoietin
- 1, 25 Vitamin D
- Renin
- Glucose
- Ammonia / Bicarbonate

Ammoniogenesis Falls With Worsening T1D



Schainuck et al, 1970

RISK FOR PROGRESSION



Adjusted for age, sex, race, diabetes, hypertension, CVD, serum potassium, BUN, calcium, anion gap, hemoglobin, baseline eGFR, insurance, and median income

Shah, Melamed, Abramowitz

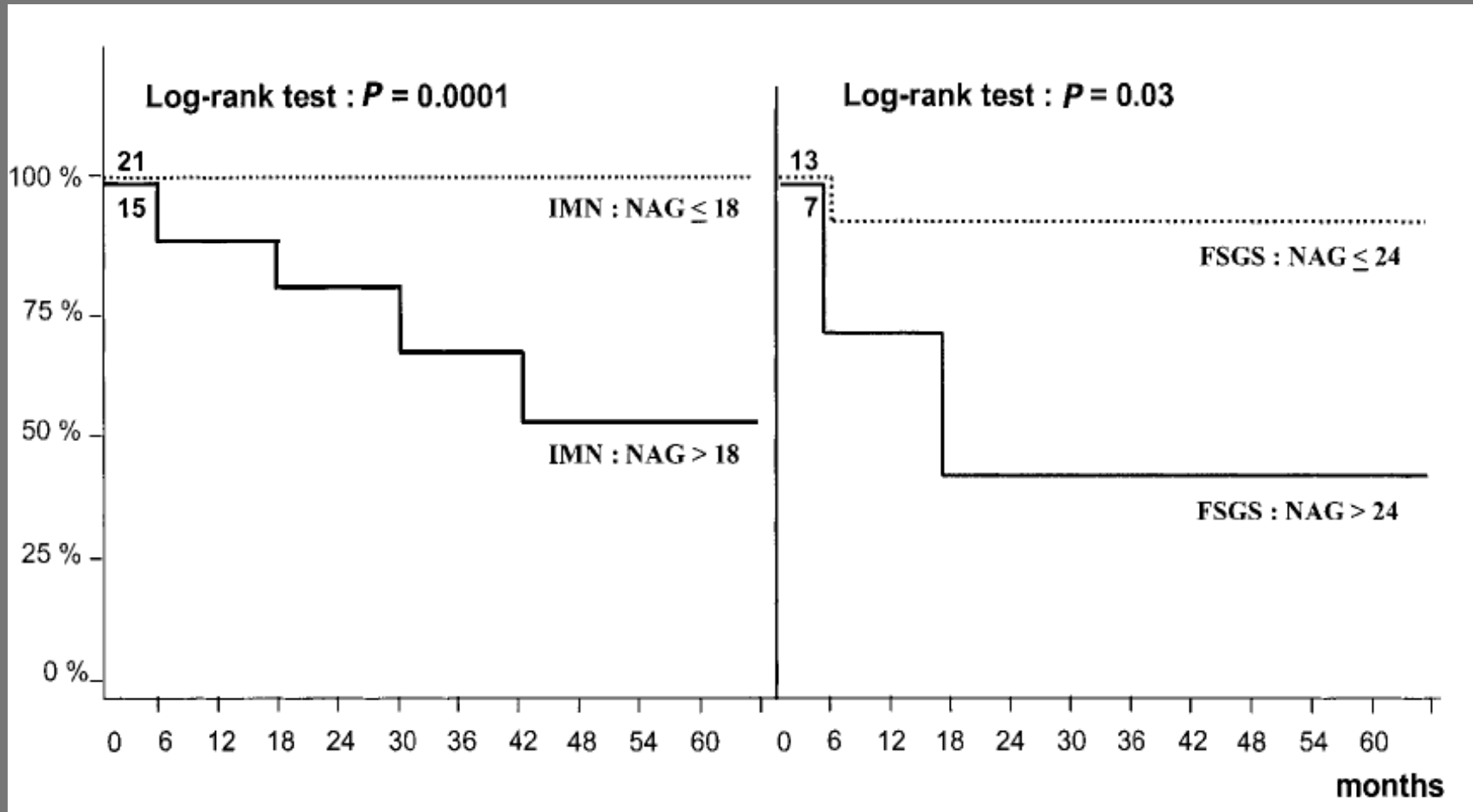
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Urinary Injury Proteins in CKD Predict Progression

- Kim-1
- NGAL
- NAG

Survival Without Doubling Serum Creatinine or ESRD and Relation to NAG



Other Injury Markers

- Cells shed from the nephron
- Gene expression in shed cells

Summary

- Clearance markers have inherent limitations but reflect major renal functions.
- Tubular dysfunctions both clearance and synthetic may yield important markers.
- Injury markers including, albuminuria, urinary cells, proteins and RNAs hold promise in CKD.
- Composites should be tested.