Diabetic Nephropathy

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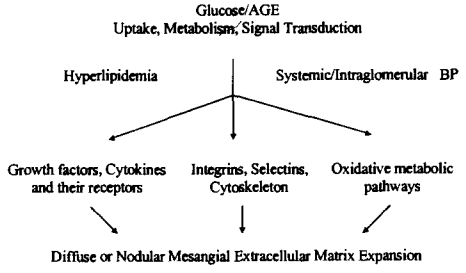
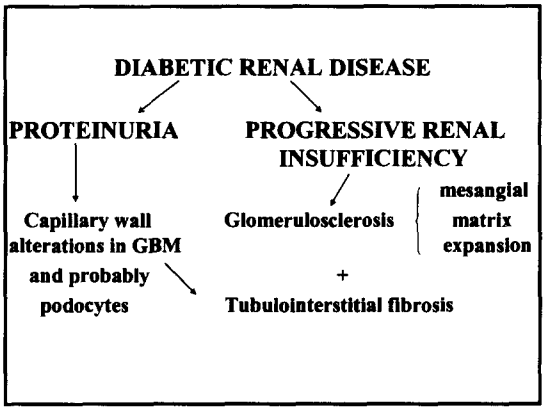
Diabetic Nephropathy

- **Diabetes is the number one cause for end-stage renal disease**
- **There are approximately 150 million diabetic patients world-wide**
- **Depending on ethnicity and glycemic control, 20-40% of these patients will require renal replacement therapy**

Pathogenesis of DN





Histopathology of the diabetic glomerulus compared to the normal glomerulus

Major ECM Components of Normal GBM and Mesangial Matrix

Glycoproteins	Proteoglycans
• Collagens IV, V, VI	• Heparan sulfate (GBM)
• Laminin	• Chondroitin sulfate (MM)
• Fibronectin	
• Nidogen/entactin	

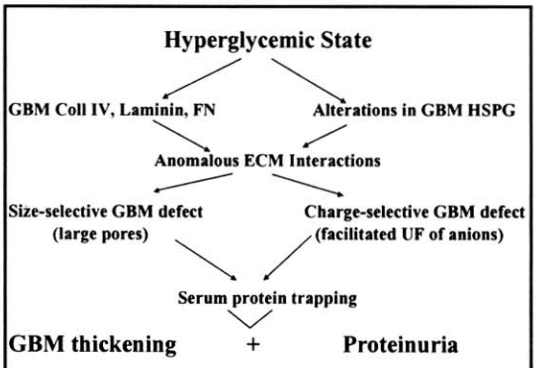
Proteinuria

ECM Pathology in Diabetic Nephropathy

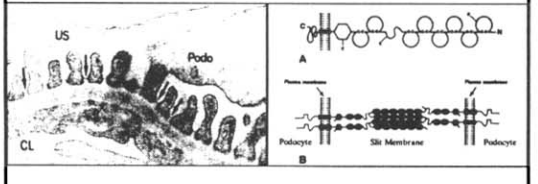
Accrual of normal ECM

Abnormal ECM physicochemical interactions

De novo expression of pathological ECM



Nephrin
A Podocyte Slit Membrane Protein



(Kawachi et al, Am J Phys, 1997)

(Ruotsalainen et al, PNAS, 1999)

Evidence for Podocyte Injury in DM

- Podocyte effacement occurs and is ameliorated by ACEi
  - *Diabetologia* 38:1197-1204, 1995
  - *J Am.Soc Nephrol.* 11:648A, 2000
- Podocyte number is diminished and correlates with albuminuria
  - *J Clin Invest.* 99:342-48, 1997
  - *J Am.Soc Nephrol.* 11:113A, 2000
  - Diabetologia 42:1341-44, 1999
- Podocytes are excreted in urine
  - NDT 15:1379-83, 2000
  - Diabetes Care 23:1168-71, 2000

Progressive Renal Insufficiency

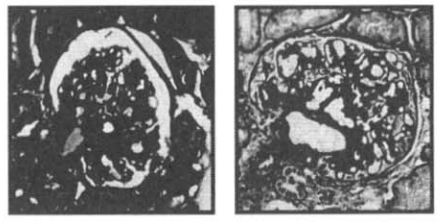
A relationship between declining creatinine clearance and expansion of the mesangium has been demonstrated in patients with Type 1 diabetes mellitus

(Mauer et al, JCI, 1984)

However, within the diagnostic categories of normoalbuminuria, microalbuminuria, and overt proteinuria, there is substantial overlap in the degree of mesangial expansion

Chavers et al: NEJM 320:966, 1989
Fioretto et al: Diabetes 43:1358, 1994

There is substantial overlap in the degree of mesangial expansion in patients classified predominantly by albuminuria



Worst normoalbuminuric Best overtly proteinuric

A Speculative Revisionist Version of the Pathogenesis of Diabetic Nephropathy

Mesangial Expansion
encroaches/occludes capillary lumen
(slow progression)
+
Podocyte Injury
apoptosis/detachment from GBM
(proteinuria and accelerated progression)
leading to
Tubulointerstitial Fibrosis/Atrophy
(final common pathway for progressive renal insufficiency)

Pathogenesis of Diabetic Nephropathy

Hyperglycemia/AGE/Glucose transport
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Role of Glucose in Mediating Mesangial Matrix Expansion

Acute Effects
AGE

Acute Effects of High Concentrations of Glucose on Mesangial Cell ECM RNA Synthesis

Increases collagen IV mRNA
Increases laminin mRNA
No change in actin "housekeeping" mRNA

(Kitamura et al Biochem Biophys Res Comm, 1992)

Glomerular Matrix Regulating Molecules
SZ Diabetic Rat, 24 wks

- MMP-1 ↓ 40%*
  - -2 ↓ 100%
  - -3 ↓ 20%*
- TIMP-1 ↑ 800%*

(Nakamura et al, JCI, 1996)

Effects of Glucose and Glucose Transport on Collagen Metabolism in Cultured Mesangial Cells

	8mM	35mM	Glut-1 Transfected
Coll synthesis	100%	170%	310%

(Helig et al, JCI, 1996)

Glycemic Control in the Management of Diabetic Patients

- After years of controversy, the DCCT trial demonstrated incontrovertibly that tight glycemic control is superior to "conventional" glycemic control in delaying and/or slowing the progression of complications in diabetes
- HbA1c in the "conventional" group averaged ~9%
- HbA1c in the intensively controlled group averaged ~7%

(DCCT, NEJM, 1993)

Oral Agents Available for Diabetes

- **Sulfonylureas**
  - glyburide, glipizide, glimepiride
- **Benzoic acid derivatives**
  - repaglinide
- **Biguanides**
  - metformin (buformin, phenformin)
- **Thiazolidinediones**
  - rosiglitazone, pioglitazone
- **α-glucosidase inhibitors**
  - acarbose, miglitol
- **Combination drugs**
  - Glucovance (glyburide + metformin)

DCCT Results for the Combined Cohort

Intensive therapy reduced the incidence of:

Microalbuminuria by 39%
Overt proteinuria by 54%

(DCCT, NEJM, 1993)

Glycemic Control in Overt Nephropathy:

There are extrarenal benefits.
Are there renal benefits?

Role for Glycemic Control in Overt Diabetic Nephropathy?

Univariate Analysis
Correlations to Rate of GFR decline
in Patients taking ACEi

MAP	r=0.58, p=0.01
Albuminuria	r=0.67, p<0.01
HbA1c	r=0.69, p<0.01
Scholesterol	r=0.51, p<0.05

(Parving, AJKD, 1990)

Consequences of Advanced Glycosylation Endproducts

Crosslinks and accumulates on proteins, altering function
Stiffens connective tissue
Interferes with tissue remodeling
Traps lipoproteins
Stimulates the synthesis of cytokines and growth factors
Promotes the accretion of ECM

Results of the Clinical Trial of the AGEi Pimagedine in the Treatment of Overt Diabetic Nephropathy

Benefits	Shortcomings
Improved proteinuria	A trend toward but no statistically significant improvement in renal function
Improved cholesterol	Increased CV morbidity/mortality in patients with NIDDM
Improved retinopathy	Systemic vasculitis in <1% of treated patients

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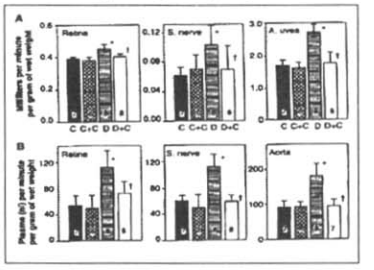
Hormones in the Pathogenesis of Diabetic Nephropathy

Hormonal effects

- diminished insulin amount or action
- increased glucagon, growth hormone, and IGF-1
- altered concentrations and/or responsiveness to:
  - angiotensin
  - prostaglandins/lipoxygenases

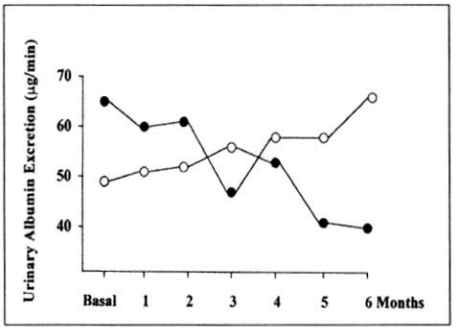
Amelioration of Hyperfiltration by Provision of C-Peptide

(Ido et al, Science, 1997)



Beneficial effects of C-peptide on incipient nephropathy and nephropathy in patients with Type 1 diabetes- A 3-month clinical study

B-L Johansson, K Borg,
E Fernqvist-Forbes, A Kernell, T Odergren,
J Wahren



(Johansson et al)

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Afferent arteriolar dilation predisposes to intraglomerular hypertension in diabetes

An experimental model linking intraglomerular hypertension to ECM accumulation

- Mesangial cells can be grown on surfaces with stretch applied to them
- Stretch may recapitulate in vitro the effects of intraglomerular hypertension in vivo
- Increasing the stretch on mesangial cells increases the synthesis of collagen mRNA and protein

(Cortes et al)

The ACEi Captopril was given to patients with IDDM and overt nephropathy to test the hypothesis that a reduction in intraglomerular hypertension would improve renal outcomes

Captopril reduced the doubling time of serum creatinine, the risk of reaching ESRD, and the risk of dying by ~50%

(Lewis et al, NEJM, 1992)

However, the data that ACEi slow progression of diabetic nephropathy in patients with Type 2 diabetes have been equivocal

Effects of ARBs on Renal Outcomes in Type 2 Diabetes

Data presented at ASH Meeting, May 2001

- Irbesartan vs amlodipine (IDNT trial)
  - slowed the serum creatinine doubling time
- Irbesartan in Microalbuminuria Trial (IRMA-2)
  - relative risk of progression from microalbuminuria to overt proteinuria reduced by 30% by the ARB; risk reduction was dose-dependent
- Losartan vs placebo add on (RENAAL trial)
  - significant reductions in time to doubling of serum creatinine and in progression to ESRD

ACE inhibitors Should be Prescribed and Monitored by an Experienced Physician

Side Effects of ACE inhibitors

Cough

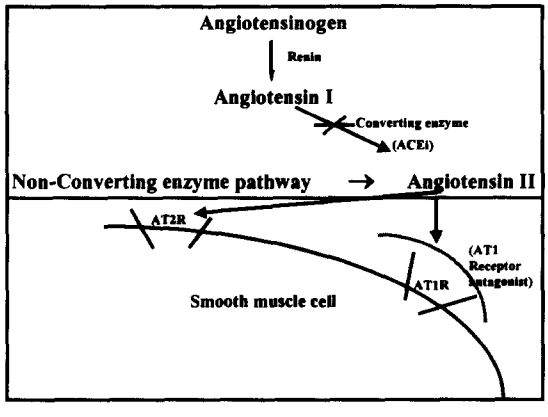
High blood potassium

Worsening of kidney function

Low white blood cell count (rare)

Harms the fetal kidney during pregnancy:

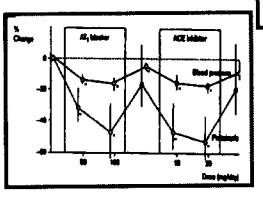
ACEI SHOULD NOT BE USED IN PREGNANCY

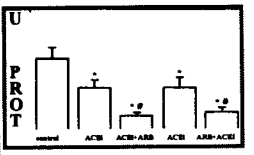


ACEi and ARBs: Comparative and Synergistic Renal Effects

ACEi and ARBs lower systemic & intraglomerular BP & proteinuria & inhibit glomerulosclerosis and tubulointerstitial fibrosis equivalently.

(Gansevoort et al KI 45:861, 1994)





In patients with IgA nephropathy, the combination of ACEi + ARBs were additive in improving proteinuria

(Russo et al AJKD 33:851, 1999)

Combination ACEi/ARB Therapy is Safe

Design:

108 patients with Ccr 20-45 ml/min
randomized to one of the following Rx x 5 wks:
Valsartan 160 mg qd
Valsartan 80 mg qd + Benazepril 5-10 mg qd
Valsartan 160 mg qd + Benazepril 5-10 mg qd

Result:

Adverse events were similar (45.5%; 33.3%; 25%)
1 patient in each group withdrew for hyperkalemia
None had ARF, high Screatinine, or hospitalization

(Ruilope et al: J Hypertension 18:89, 2000)

What should be the blood pressure goal in treating patients with diabetic nephropathy?

- Goal might be determined by picking a value beyond which proteinuria no longer declines rapidly. MAP ~98 has been suggested by Aurrell et al, KI, 1992
- Goal might be determined by picking a value beyond which GFR slowing diminishes . MAP ~92 suggested by Petersen et al, Ann Int Med, 1992
- Goal might be chosen where ACEi therapy no longer is advantageous over non-ACEi therapy. MAP~98 (unpublished observation)

Goal BP/CV Management in Patients with Diabetic Nephropathy

MAP $\leq$ 92 mm Hg
BP $\leq$ 125/75
Requires on average the use of 3-4 antihypertensive agents
Regimen should take into account that cardiovascular disease is the predominant killer in this population
(ACEI/ARB, beta-blocker, diuretic, Ca channel blocker)
Adjunctive therapy with diet, exercise, weight loss, ASA and HMG-CoA reductase inhibitors

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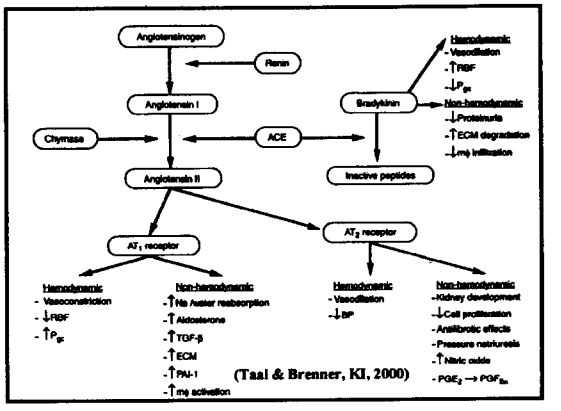
Genetic predisposition



(Taal & Brenner, KI, 2000)

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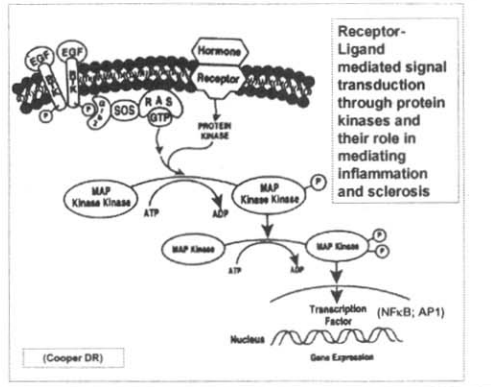
Experimental Diabetes induces the Expression of mRNAs for many Growth Factors

TGF-β
TNFα
PDGF-B
FGF
PCNA

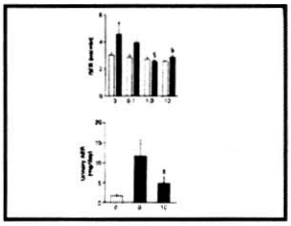
(Nakamura et al, Diabetes, 1993)

PKC and its Role in the Pathogenesis of Diabetic Nephropathy

A II Thromboxanes LDL
↓
Phosphoinositide hydrolysis
↓
↑ DAG ← de novo synthesis → ↑ Glucose
↑ PKC
↑ TGF-β
↑ ECM synthesis



Effect of PKC-beta Inhibition on GFR & Proteinuria in Rats with Streptozotocin Induced Diabetes



Ishii et al, Science 272:728, 1996

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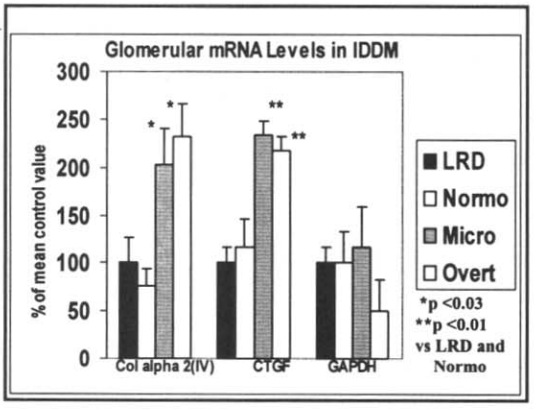
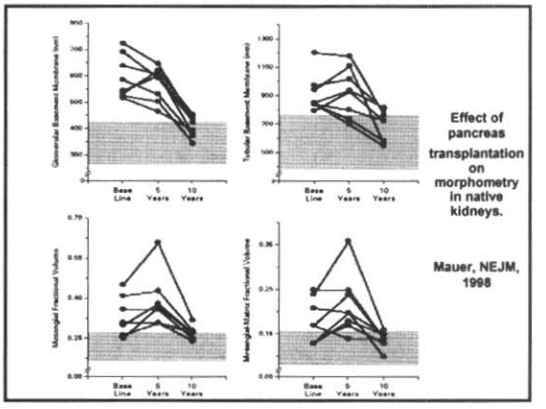
Patients with IDDM, normoalbuminuria and normotension may already have mesangial expansion

(Chavers et al, NEJM, 1989)

Glomerular mRNA profiles for ECM molecules and growth factors differentiate diabetic nephropathy from healthy kidney and demonstrate biochemical equivalence between glomeruli of patients with microalbuminuria and overt nephropathy in Type 1 diabetes.

These data suggest that microalbuminuria, rather than being a "predictor" of diabetic nephropathy, is instead an earlier phase of it. (Adler et al, KI, 2000)





Renal Function after Pancreas Transplantation
(Mauer et al, NEJM, 1998)

Urinary Albumin Excretion			Creatinine Clearance			
Base Line	5 yr	10 yr	Base Line	1 yr	5 yr	10 yr
mg/24 hr			ml/min/1.73 m²			
7	2	6	138	75	82	83
8	4	23	113	71	63	68
12	21	43	101	61	86	91
86	6	6	116	86	91	78
120	80	48	128	61	90	89
127	155	18	84	49	44	50
278	126	20	110	54	72	67
1276	40	176	78	65	68	67
103*	30*†	20*‡	108±20	65±12§	74±16§	74±14§

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The Genetic Approaches

- Look for the role of genes which are already suspected as causing diabetic kidney disease
  - Candidate gene approach
- Scan the entire human genome looking for new and unsuspected genes which may be important

ACE II/DD Polymorphism and the Stages of Diabetic Nephropathy

%

	none	μalbuminuria	overt	advanced
DD	31	35	35	37
ID	44	48	50	51
II	25	17	15	12

(Marre et al, JCI, 1997)

Chromosomal Regions Suspected to Predispose to Diabetic Nephropathy

3*,7,9,20

(Imperatore et al, Diabetes, 1998)

*(Krolewski et al, KI, 1999)

PHASE 1	PHASES 2 & 3	PHASE 4
No nephropathy	Overt/incipient nephropathy	ESRD
Preventive therapy	Definitive/Palliative therapy	Replacement therapy
↓	↓	↓
Tight glycemic control	Tight glycemic control	Hemodialysis
Moderate dietary protein restriction	ACEI/AT1RA	CAPD
	Other antihypertensives	Renal transplantation
	Tighter protein restriction?	Pancreas Transplantation

Therapies Currently under Investigation for Diabetic Nephropathy

- AGE inhibitors (?) /blockers / breakers
- PKC inhibitors
- New agents to modulate hemodynamics / hypertrophy / hyperplasia / ECM synthesis
- Growth factor / cytokine / signal transduction inhibition