Polycystic Kidney Disease: an Update

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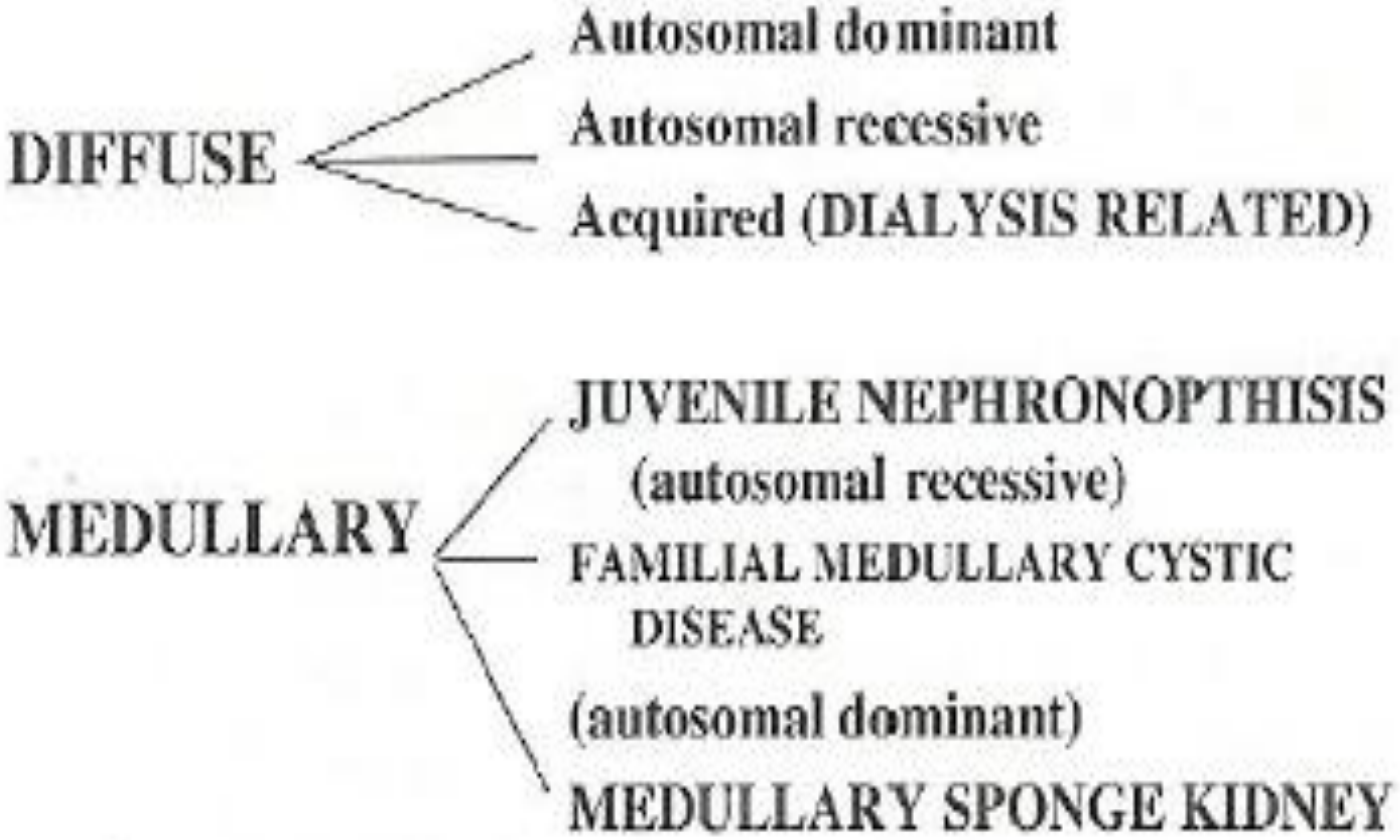
athens-NEPHROLOGY

Classification of Primary Renal Cystic Diseases



Misc: Von Hipple Lindau, Tuberous sclerosis, renal

ADPKD

- Most common genetic disease
  - Incidence 1:500 – 1:1000 live births

- Clinical Manifestations
  - abdominal mass
  - chronic flank or back pain
  - gross hematuria
  - recurrent UTI
  - nephrolithiasis (uric acid stones)

Ultrasound Criteria for Diagnosis of PKD1 in At-Risk Individuals

Positive and negative predictive values 97-100%

Ravine et al, Lancet 343:824, 1994

- Age < 30: at least 2 cysts (unilateral or bilateral)
- Age 30-59: at least 2 cysts/kidney
- Age ≥ 60: at least 4 cysts/kidney

- For PKD2 age 30-59, use 4 or more cysts in both kidneys for sensitivity of 96%

Pei et al, JASN 14:107A, 2003

Differential Dx of Cystic Kidney Disease

- Multiple simple cysts
- Autosomal recessive polycystic kidney disease
- Tuberous sclerosis
- von Hippel-Lindau disease
- Acquired cystic disease
- Familial Juvenile Nephronophthisis-Medullary Cystic Disease
- Oro-facio-digital syndrome type 1
- Glomerulocystic kidney disease
- Hajdu-Cheney syndrome

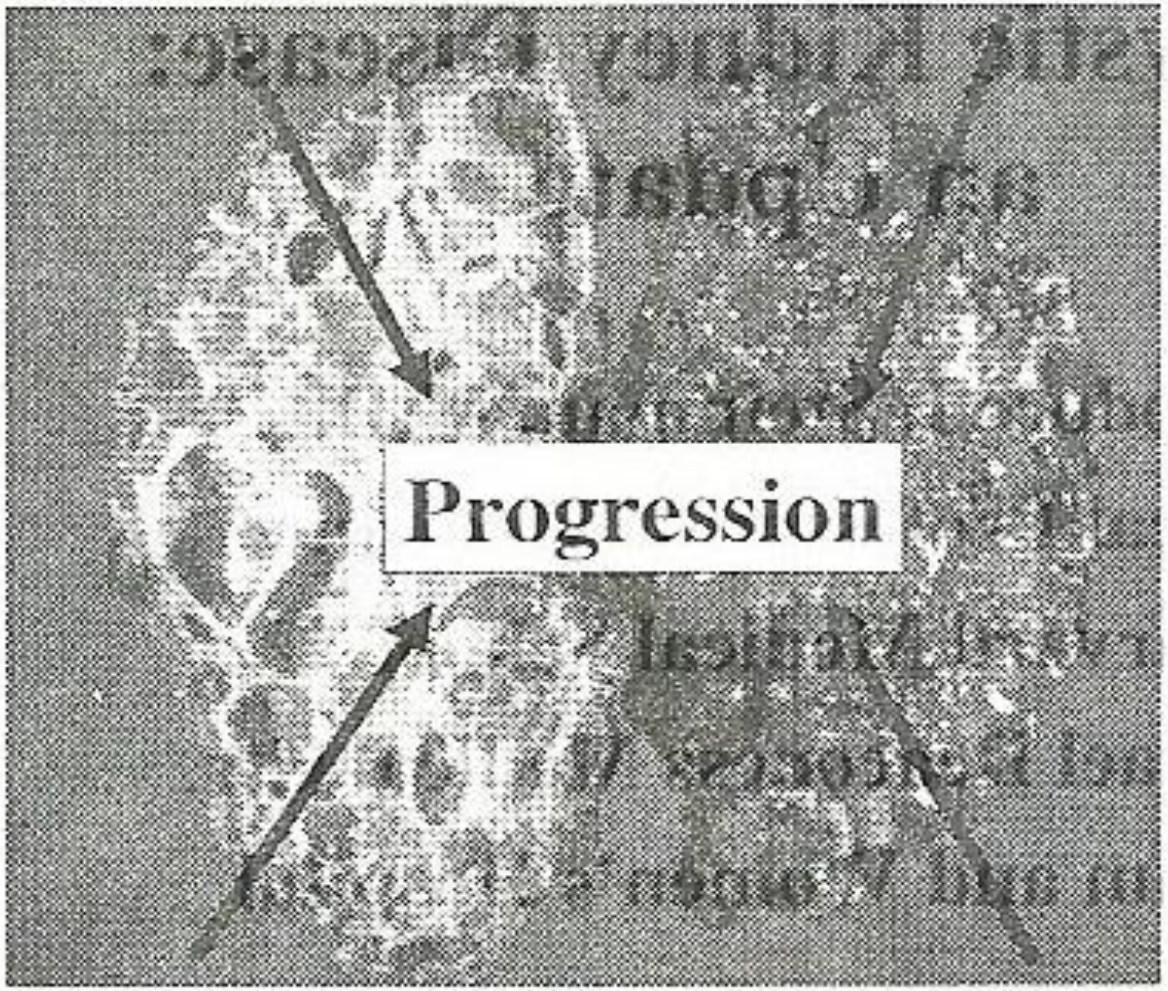
Autosomal Dominant Polycystic Kidney Disease

- Mutation in 85-90% located on short arm of chromosome 16p 13.3 – p13.1 – (PKD1 locus)

- 10% - 15% of mutation is located on chromosome 4q21-q23 milder phenotype with PKD2 locus. Later age of diagnosis and hypertension, smaller kidney volume, fewer kidney cysts, later age of ESRD system: disorder is kidney, liver, pancreatic and vascular abnormalities.

Germline mutations

Modifying genes



Peters and Breuning. Lancet, 2001

Environmental factors

Somatic mutations

Pathogenesis of Cyst Formation "Second Hit" Hypothesis

- Although germline mutations are present in all renal tubule cells, cysts develop in only a tiny fraction of them.
- Germline mutation in polycystin 1 or polycystin 2 must be present.
- Somatic mutation ("second hit") necessary for initiation of cyst formation
  - Sequence
    1. Germline mutation inactivates one copy of PKD1
    2. Somatic mutation or deletion inactivates the remaining wild-type normal copy of functional polycystin

Pei et al. JASN 1999; 10:1524-1529

Angiogenesis in ADPKD

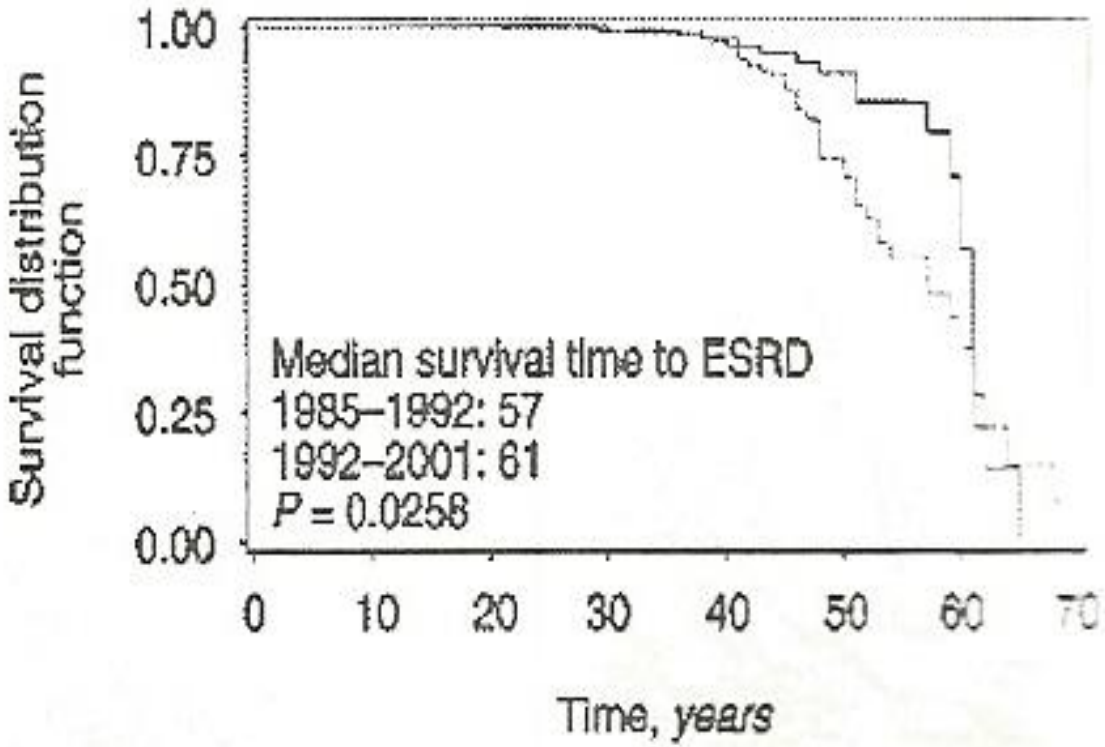
- Angiogenesis refers to the growth of blood vessels: arteries. veins. capillaries.

- The role of angiogenesis has been recognized in the field of cancer biology; tumors cannot grow without growth of blood vessels to provide nutrients. Angiogenesis inhibitors are now employed for the treatment of cancer.

- New data from Dr. Bello-Reuss have been published demonstrating large numbers of highly abnormal blood vessels around cysts.

Angiogenesis in ADPKD (2)

- Since the enlargement of cysts depends both on the growth of cells lining the cysts and the secretion of fluid into the cysts, delivery of oxygen and nutrients is essential for this to happen.
- Therapies targeting angiogenesis *may* be of value in slowing or preventing the expansion of cysts.
- Grants addressing angiogenesis in PKD animal models will be funded by PKDF.



Survival time to ESRD for 158 female ADPKD subjects examined between June 1985 and May 1992 (dashed line; median 57 years) vs. 178 female ADPKD subjects examined between June 1992 and May 2001 (solid line; median 61 years; P = 0.0258).

Kidney International, Vol. 63 (2003), pp. 678–685

Epidemiological study of kidney survival in ADPKD

ROBERT W. SCHRIER, KIMBERLY K. MCFANN, and ANN M. JOHNSON

Effect of Angiotensin Blockade

- **In animal models of PKD**
  - reduced kidney size by about 10-50%
  - Preserved kidney function
- **In human kidney disease, other than ADPKD**
  - Effective in slowing progression of kidney diseases typically associated with protein in the urine, diabetes and nephritis
  - Effective in slowing progression of kidney disease in African Americans with hypertension
- **In ADPKD, has not been shown to slow progression of kidney disease. However, effective in preventing thickening of the heart muscle (LVH: left ventricle hypertrophy)**

HALT-PKD in Progress (Halt Progression of Autosomal Dominant Polycystic Kidney Disease)

Objective: Two concurrent, randomized, double-blinded controlled trials to assess the effects of multi-level blockade of the renin-angiotensin-aldosterone system (RAAS) and aggressive blood pressure control on progression of early (NKF Stage 1-2) and late (NKF Stage 3) ADPKD

Hypotheses:

1. Blockade of RAAS will significantly reduce renal progression as compared to other antihypertensive therapy
2. Lower blood pressure will significantly reduce renal progression as compared to standard BP targets

Tolvaptan in Human ADPKD

- Phase II studies (safety, dosing, side effects) completed)
- Pharmacokinetic profile similar to healthy control population
- Well tolerated with few side effects
- Effective blockade of the AVP V_2 receptor defined as Uosm <300 mOsm/kg

– Personal communication: Dr. Vicente Torres

Artificial
Organs

Adult Polycystic Kidney Disease: Who Needs Hospital Follow-Up?

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BACKGROUND

- Previous studies have identified several factors to be associated with deterioration of renal function in patients with adult polycystic kidney disease (APKD). These include the nature of the mutation (PKD1 deteriorating faster than PKD2), male gender, the onset of hypertension below the age of 35y, haemoglobin concentration and hyperlipidaemia.

Aim

- The present retrospective study was undertaken further to examine the contribution of these factors to deterioration in renal function.
- Additionally, an attempt was made to determine whether hospital follow-up was necessary in the early decades of this disease in all patients or whether this could be more selective with beneficial cost savings.

METHODS

- The *clinical data* of 184 patients with APKD attending a dedicated clinic were reviewed. Of these, 120 of them satisfied criteria for inclusion in this study.

Exclusion criteria: age less than 18 years,
follow up for a period of less than 3 months,
less than four data points to calculate change in estimated glomerular filtration rate with time (ΔeGFR, ml/min/1.73m^2/y).

METHODS

- Gender and age were recorded.
- Patients were classified by race into white, black, indo-asian and oriental.
- Seated systemic arterial blood pressure (systolic, diastolic and mean), recorded at the time of first clinic attendance.
- Initial laboratory estimation of haemoglobin, cholesterol and creatinine concentrations.

METHODS

- In each case, estimated glomerular filtration rate (eGFR) was calculated using the 4-variable form of the Modification of Diet in Renal Disease (MDRD) formula. Using the same method, the eGFR at successive time points during follow-up of each patient was calculated.
- The patients were then classified into those who had a statistically significant ($p<0.05$) average rate of deterioration in renal function ($-\Delta eGFR$) and those who did not.

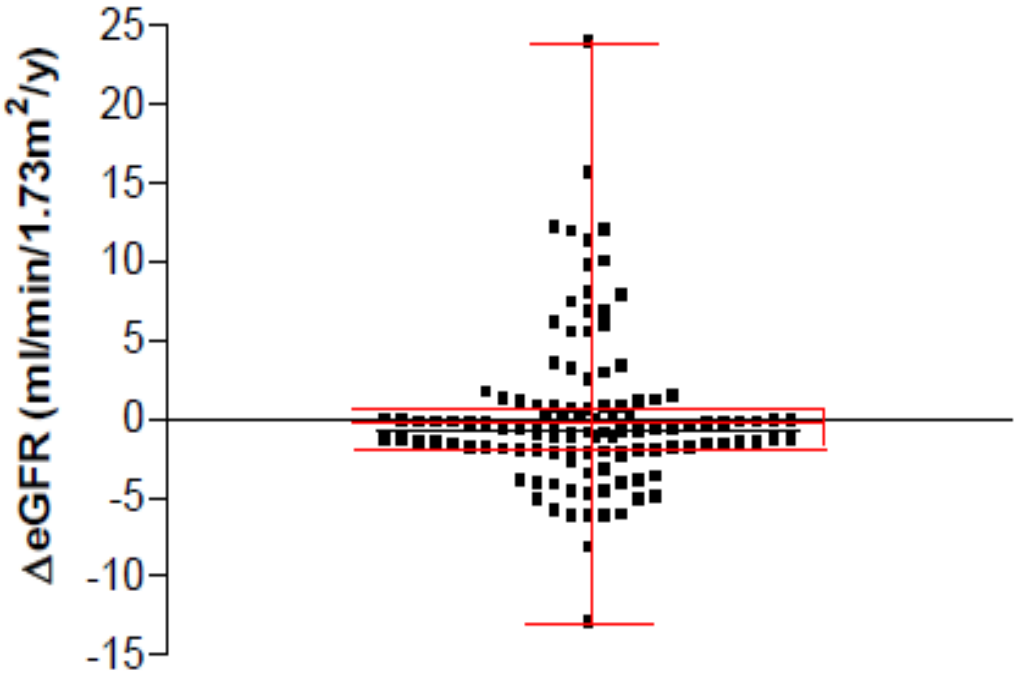
RESULTS

Characteristics of patients. Patients were subsequently split into two groups: those without and those with statistically significant annual deterioration in eGFR whose characteristics were then compared statistically.

Variable (units)	All patients	Those *without* a statistically significant annual deterioration in eGFR (=ΔeGFR)	Those *with* a statistically significant annual deterioration in eGFR (=ΔeGFR)	p value
Number (n)	120	94 (78%)	26 (22%)	-
Median ΔeGFR [range] (ml/min/1.73m^2/y)	-0.8 [-17.25 to +23.9]	-0.2 [-17.25 to +23.9]	-2.6 [-6.2 to -0.7]	p<0.0001
Male/Female	47/73	33/61	14/12	p=0.26
Mean age ±SD (y)	36.7±12.7	36.6±13.0	36.7±11.6	p=0.97
Race: White/Black/Asian (n)	103/7/10	80/6/8	23/1/2	p=0.32
Median duration of follow-up [range] (months)	58 [3 to 172]	46 [3 to 161]	86 [23 to 172]	p=0.002
Mean initial Hb±SD (g/dl)	13.6±1.5	13.7±1.4	13.4±1.7	p=0.42
Mean initial cholesterol±SD (mM/l)	4.86±1.1	4.88±1.1	4.81±1.0	p=0.84
Mean initial eGFR±SD (ml/min/1.73m^2)	74.2±18.2	73.2±17.4	78.0±21.0	p=0.25
Mean systolic BP±SD (mmHg)	146±21	148±21	128±11	p=0.02
Mean diastolic BP±SD (mmHg)	82±11	82±12	78±5	p=0.07
Mean MAP±SD (mmHg)	104±13	105±13	95±5	p=0.04

RESULTS

Distribution of ΔeGFR for all patients with APKD: median = -0.8ml/min/1.73m²/y; (IQR= -2.1 – 0.8; range= -17.2 – 23.9).



RESULTS

- No statistically significant differences in initial haemoglobin or cholesterol concentrations or eGFR values were found between the groups.
- There was a trend for initial systolic, diastolic and mean arterial blood pressure values to be lower in the group of patients destined to develop deteriorating renal function but differences failed to achieve *a priori* levels of statistical significance.

RESULTS

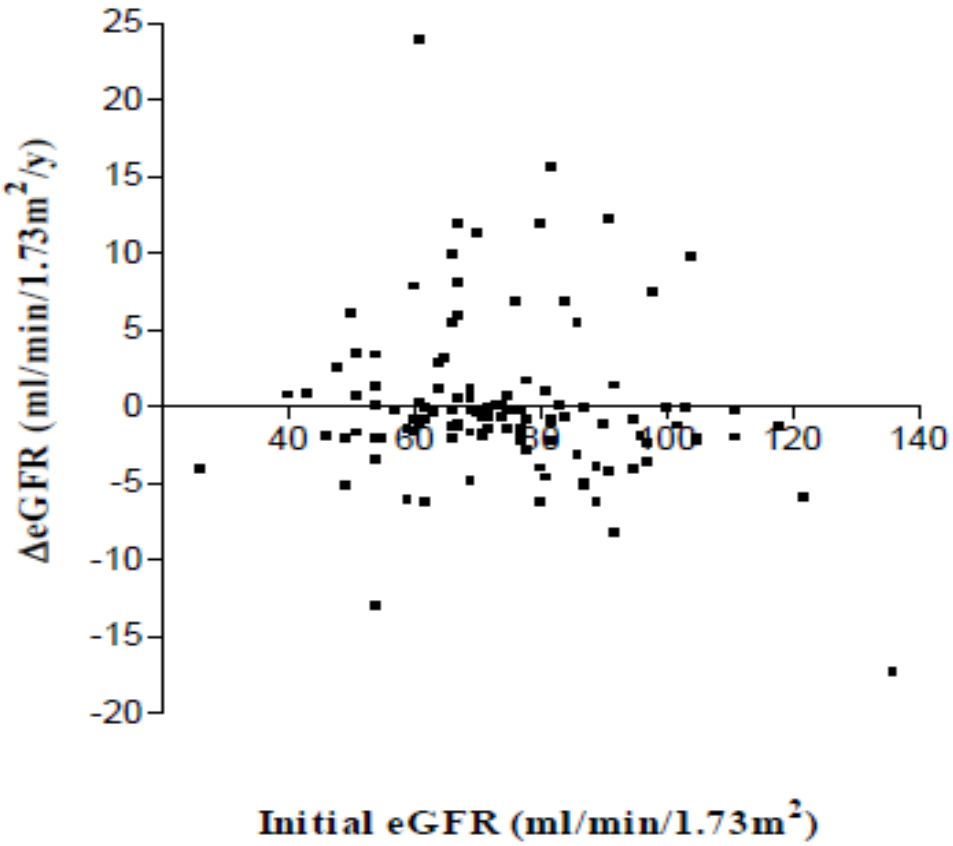
Rank correlations between ΔeGFR and other variables

Variable (Units)	Number of paired values	Spearman's *rho*	Probablility
Duration of follow-up (months)	120	-0.07	p=0.48
Initial eGFR (ml/min/1.73m^2)	120	-0.19	p=0.04
Initial Hb (g/dl)	100	0.09	p=0.35
Initial cholesterol (mM/l)	53	0.05	p=0.74
Initial PTH (pg/ml)	7	0.22	-
Initial Systolic BP (mmHg)	55	0.11	p=0.44
Initial Diastolic BP (mmHg)	55	0.12	p=0.39
Initial MAP (mmHg)	55	0.18	p=0.18

RESULTS

ΔeGFR (ml/min/1.73m²/y) vs. initial eGFR (ml/min/1.73m²).

Spearman's *rho*= -0.19, p=0.04



CONCLUSIONS

- There was no difference in initial age, gender or racial distribution or in initial eGFR between the groups destined to develop deteriorating renal function and those that would not develop this.
- Age at the time of presentation did not seem to predict subsequent deterioration.

CONCLUSIONS

- Only those patients with polycystic kidney disease with a statistically significant annualized decrease in eGFR may need to be referred for hospital follow up in the renal clinic.
- Some compromise could be necessary concerning control of blood pressure in some patients.
- Overenthusiastic antihypertensive treatment could accelerate deterioration in renal function while protecting against development of generalized vascular disease.

CONCLUSIONS

- In those patients with rather stable renal function over the follow-up period, no significant correlation was found between age of patients, duration of follow up and ΔeGFR.
- That means that patients, who for unknown reasons do not develop significant decline in their renal function for a period of 5 years, probably do not usually need the care of a specialist.

Predictors of Disease Progression (MR)

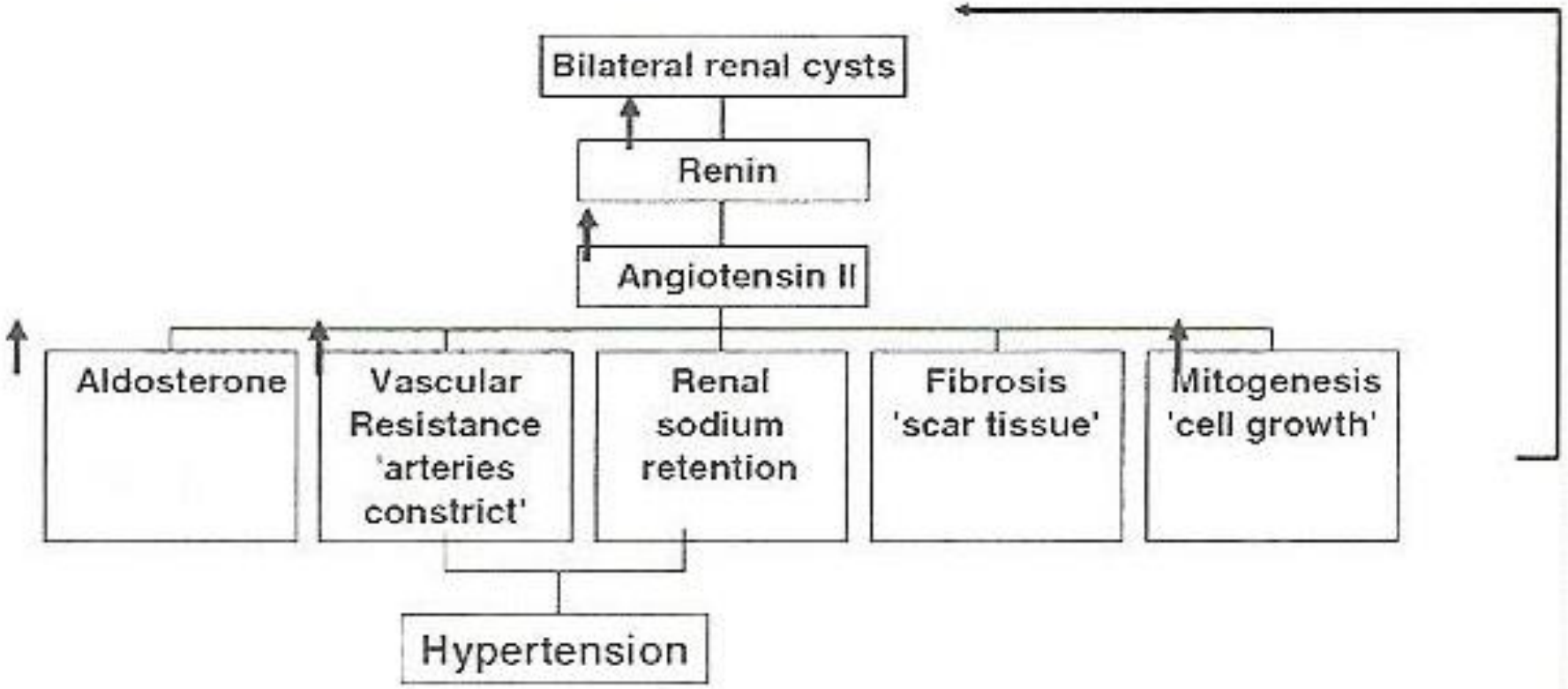
- Hemodynamic
  - RBF
  - RVR
  - GFR
- Anatomic
  - Total kidney volume
  - Total cyst volume
  - % cyst volume

CRISP Study KI 2003,64:2214-2221

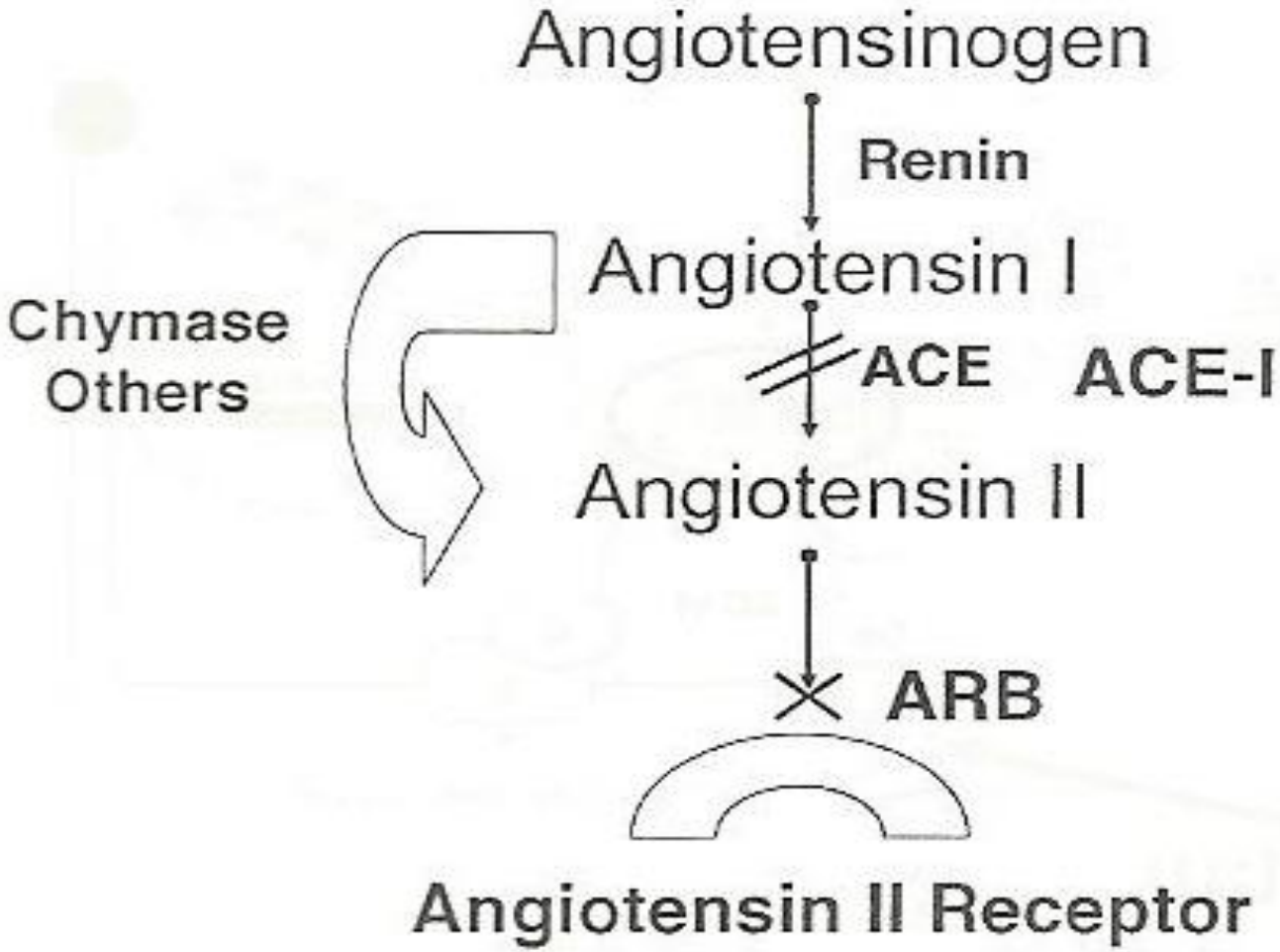
Renal hemodynamic parameters are the strongest predictors of renal function

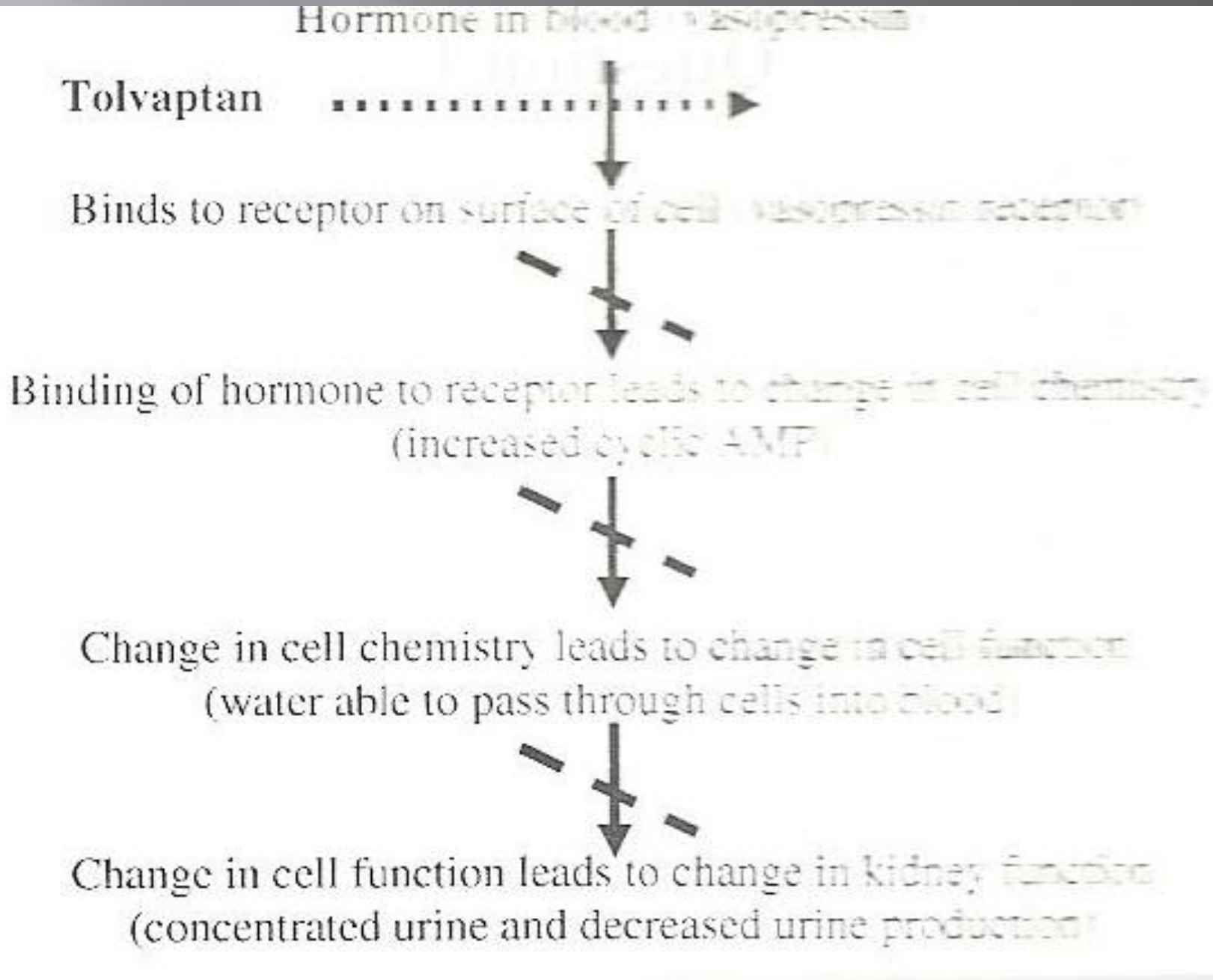
Renal volume and rate of renal volume growth are secondary markers of disease progression

Activation of the RAAS in PKD



Multilevel Blockade of the RAAS




Tolvaptan

New Therapies On the Horizon

Animal Studies

- Corticosteroids
- Paclitaxel (Taxol)
- Potassium bicarbonate or potassium citrate
- Lovastatin
- Inhibitors of Caspase
- PPARg (peroxisome proliferator) inhibitors
- Roscovitine

Human Studies

- Inhibitor of EGFR tyrosine kinase activity (EKI-785)
- Sirolimus
- Angiotensin blockade
- Somatostatin
- Inhibition of vasopressin V2 receptor (OPC31260; OPC41061 (Tolvaptan))