Obesity and the kidney

Does obesity injure the kidney?

Avry Chagnac

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The Role of Obesity in the Initiation and Progression of CKD

The nephrotic syndrome: a complication of massive obesity

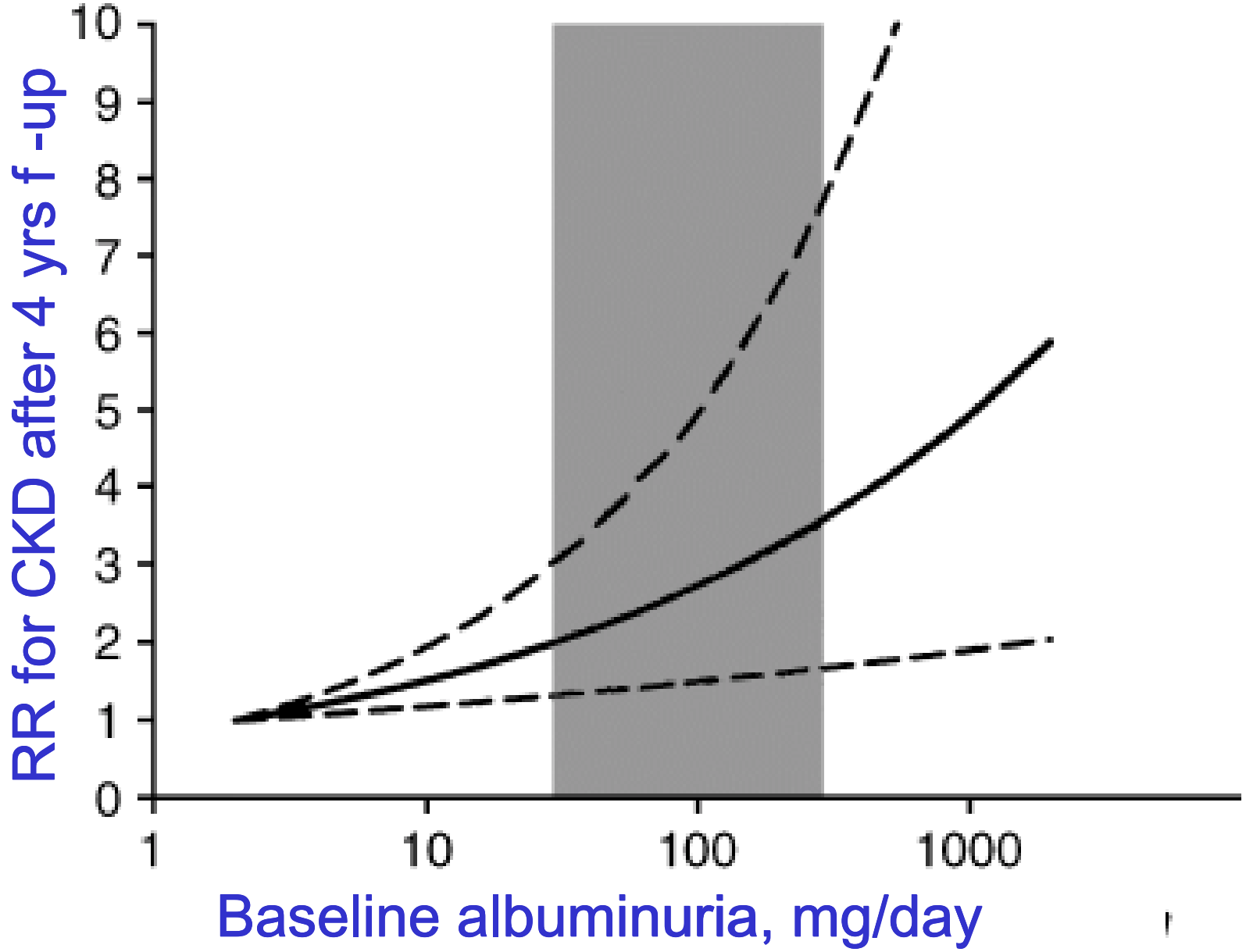
Weisinger JR, Kempson RL, Eldridge FL, Swenson RS.

Ann Intern Med. 1974 Oct;81(4):440-7

The Role of Obesity in the Initiation and Progression of CKD

1998: Cirillo et al, Arch Int Med
Obesity is an independent risk factor for microalbuminuria in non-diabetic subjects
RR 1.3-1.8 / 4 units BMI

Albuminuria as a predictor of CKD in the general population (PREVEND study). Verhave: Kidney Int 2004



The metabolic syndrome and CKD in the US population
Chen: Ann Intern Med 2004

- NHANES III: 1988-1994
- >6000 participants
- Outcome measures:
  - Microalbuminuria> 30 –300 mg/g creat
  - Macroalbuminuria> 300 mg/g creat
  - CKD= GFR (MDRD)< 60 ml/min

Metabolic syndrome

NCEP ATPIII:

3 or more of the following:

- Abdominal obesity (waist 102 cm M / 88 cm F)
- TG ≥ 150
- Low HDL (<40 M; <50 F)
- BP ≥ 130/85
- Fasting serum glucose ≥ 110

The metabolic syndrome and CKD in the US population
Chen: Ann Intern Med 2004

- Prevalence of metabolic syndrome (MS): 24.7%

	MS-	MS+	
Microalbuminuria	4.7%	12.3%	x2.5
Macroalbuminuria	0.4%	1.6%	x4

The metabolic syndrome and CKD in the US population
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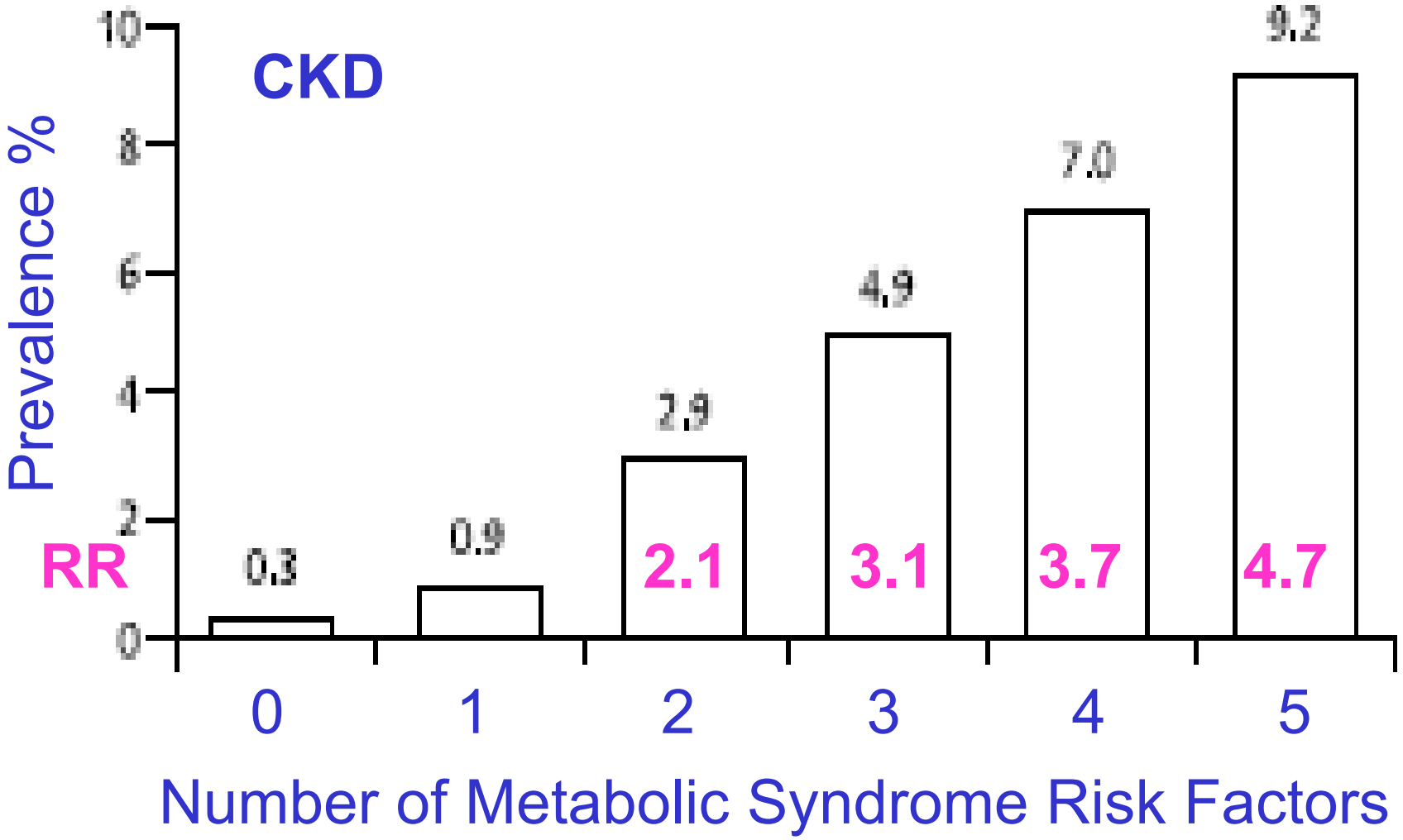
- Prevalence of metabolic syndrome (MS): 24.7%

	MS-	MS+	
Microalbuminuria	4.7%	12.3%	x2.5
Macroalbuminuria	0.4%	1.6%	x4
CKD	1.2%	6%	x5

The metabolic syndrome and CKD in the US population
Chen: Ann Intern Med 2004

RR for CKD

High BP	2.4
High TG	1.6
Low HDL	1.9
Fasting glucose	1.2
Abdominal obesity	1.5
Metabolic Syndrome	2.2



Chen: Ann Intern Med 2004

The metabolic syndrome and CKD in the US population
Chen: Ann Intern Med 2004

RR for CKD excluding diabetics

High BP	2.9
High TG	1.9
Low HDL	2.2
Abdominal obesity	2.0
Metabolic Syndrome	2.8

Association between BMI and CKD in apparently healthy men Gelber et al, AJKD, Nov 2005

- Physician's Health Study: >22,000 men recruited in 1980's
- 11,104 gave blood samples in 1996 for Cr measurement
- Age at baseline: 53±8
- Mean follow-up: 14 yrs
- CKD: GFR<60 ml/min/1.73 m^2
- CKD at follow-up: 12.4%

Association between BMI and CKD in apparently healthy men
Gelber et al, AJKD, Nov 2005

BMI quintiles	% with GFR<60
<22.7	9.5
22.7-23.7	11.9
23.8-25	12.3
25.1-26.6	14.2
>26.6	14

Association between BMI and CKD in apparently healthy men
Gelber et al, AJKD, Nov 2005

RR for CKD (gfr<60) according to baseline BMI

BMI quintiles	Model
<22.7	1.0
22.7-23.7	1.13
23.8-25	1.15
25.1-26.6	1.32
>26.6	1.26

RR independent of: age, smoking, alcohol,family h/o mi, HTN, DM, chol, CV disease

Association between BMI and CKD
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Gelber et al, AJKD, Nov 2005

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Association between BMI and CKD in apparently healthy men Gelber et al, AJKD, Nov 2005

- RR for CKD with GFR<50: RR increased to 1.6
- Analysis with BMI<30 (only 4%>30): RR increased ≅

Association between BMI and CKD in apparently healthy men Gelber et al, AJKD, Nov 2005

- RR for CKD with GFR<50: RR increased++ (RR 1.6)
- Analysis with BMI<30 (only 4%>30): RR increased
- Subjects whose BMI increased by >10% during f-up:
  - Baseline normal weight: RR 1.25
  - Baseline obese: RR 2.7

Obesity and prevalent and incident CKD….
Kramer AJKD, Oct 2005

HDFP: Hypertension Detection and Follow-up Program
159,000 subjects screened (1973-4)

10,940 had diastolic BP>90 mm Hg at second visit

Data for present analysis:
BMI, proteinuria, SCr at baseline and at year 5.
N= 7,240

CKD= proteinuria + or GFR<60 (MDRD)

Obesity and prevalent and incident CKD….
Kramer AJKD, Oct 2005

Baseline data:

- N BMI: 27%
- Overweight: 41%
- Obese: 32%

All HTN: mean 157/100; no diff between groups

Obesity and prevalent and incident CKD….
Kramer AJKD, Oct 2005

Multivariate analysis:
Age, sex, race, DM, BP

After exclusion of subjects with baseline CKD and DM
The RR for incident CKD at year 5

N BMI:	1.00
Overweight:	1.22 (1.05-1.43)
Obese:	1.38 (1.17-1.63)

High risk for CKD!

What about ESRD?

BMI and risk of ESRD
Hsu: Ann Intern Med 2006

- 350, 000 adults followed for 15-35 years
- 1471 cases of ESRD

BMI and risk of ESRD
Hsu: Ann Intern Med 2006

RR after adjustment for:
age, sex, race, education, smoking, cholesterol
coronary disease, proteinuria, S creat, BP and DM

BMI	RR
18.5-24.9:	1.0
25 – 29.9:	1.7
30 – 34.9:	3.0
35 – 39.9:	4.7
>40:	5.0

These epidemiologic studies show that:

- Obesity markedly increases the risk of developing CKD regardless of the presence of DM (up to x5)
- The risk for developing CKD increases by 20% to 40% in overweight people
- The risk may also increase in people with "normal" weight and increased fat mass

Obesity-related glomerulopathy (ORG): an emerging epidemic
Kambham, D'Agati: Kidney Int, 2001

ORG defined as

- Obesity
- Proteinuria and/or Renal Failure
- Glomerulomegaly
  ± Focal Segmental Glomerulosclerosis (FSGS)
- After exclusion of other causes of FSGS

Obesity-related glomerulopathy (ORG): an emerging epidemic
Kambham, D'Agati: Kidney Int, 2001

- From 1/1986 to 4/2000: 6818 native kidney biopsies
  - 1986-1990: ORG=0.2%
  - 1991-1995: ORG=1.2%
  - 1996-2000: ORG= 2%

Incidence x10

- 71 out of 103 cases with adequate clinical data

Obesity-related glomerulopathy (ORG): an emerging epidemic
Kambham, D'Agati: Kidney Int, 2001

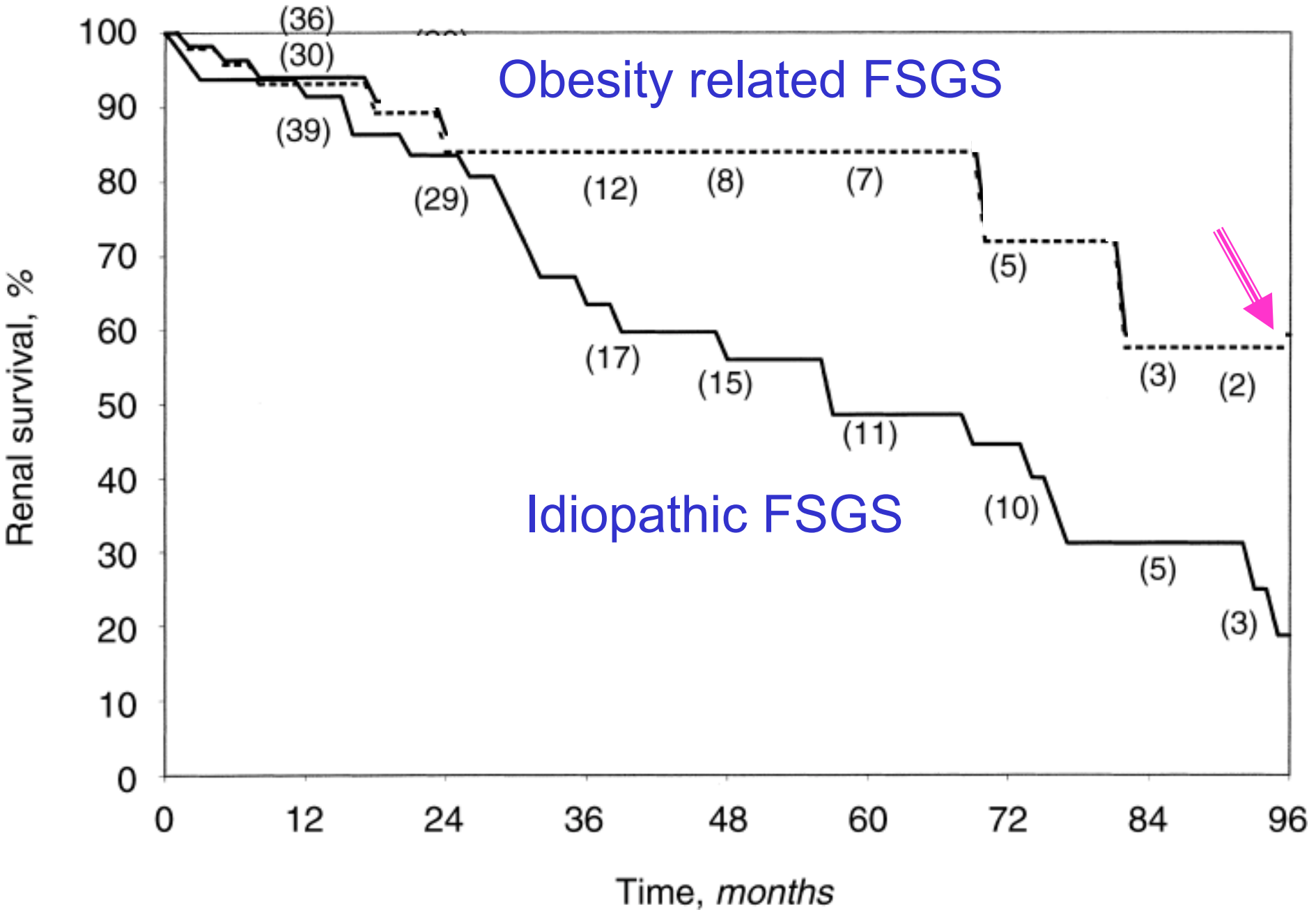
Age	42 (8-71)
Male	62%
BW	81-186
BMI	42 (31-63) (46% BMI<40)
DM	13% Mean duration 5 yrs(1-26)
HTN	62%
S.creat	1.5 mg/dl (0.6-6.3)
CRF	56%
Proteinuria	4.1 g/d (1-32)
Proteinuria>3.5g/d	48%
S.albumin	3.9 mg/dl
Nephrotic syndrome	6%

Obesity-related glomerulopathy (ORG): an emerging epidemic
Kambham, D'Agati: Kidney Int, 2001

Obesity related FSGS vs Idiopathic FSGS

- Proteinuria less severe (4.2 vs 6.9 g/d)
- Serum albumin higher (3.8 vs 2.9mg/dl)
- Less edema
- Lower serum chol (231 vs 335 mg/dl)

- More glomerulomegaly (100% vs 10%)



Kambham, D'Agati: Kidney Int, 2001

Pathogenesis

- Hyperfiltration (High GFR and FF; ± High RPF)
- Hypertension
- Overactivity of Renin AII Aldosterone (systemic; local)
- TGF
- Mesangial lipotoxicity
- Tubular lipotoxicity (FFS bound to filtrated albumin)
- Oxidative stress
- Insulin toxicity: affects glomerular hemodynamics
  - increases glomerular volume
  - potentiates Ang II actions
  - pro-inflammatory
  - …

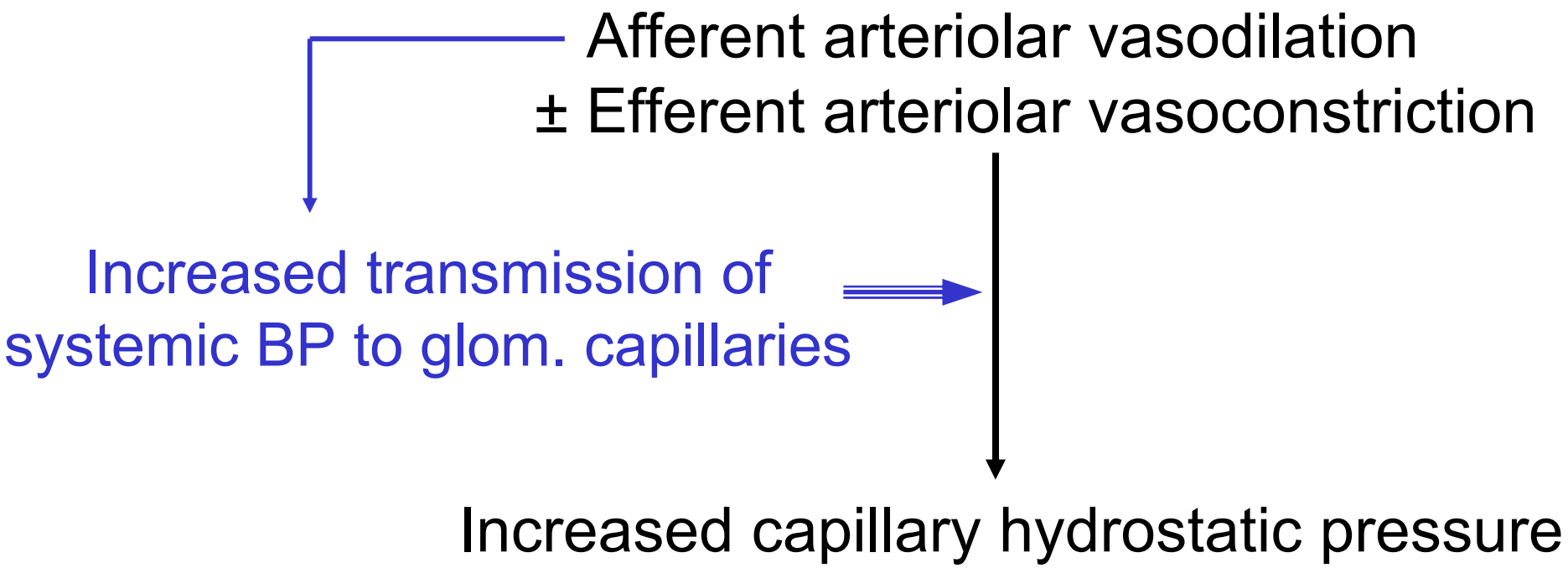
Glomerular hyperfiltration

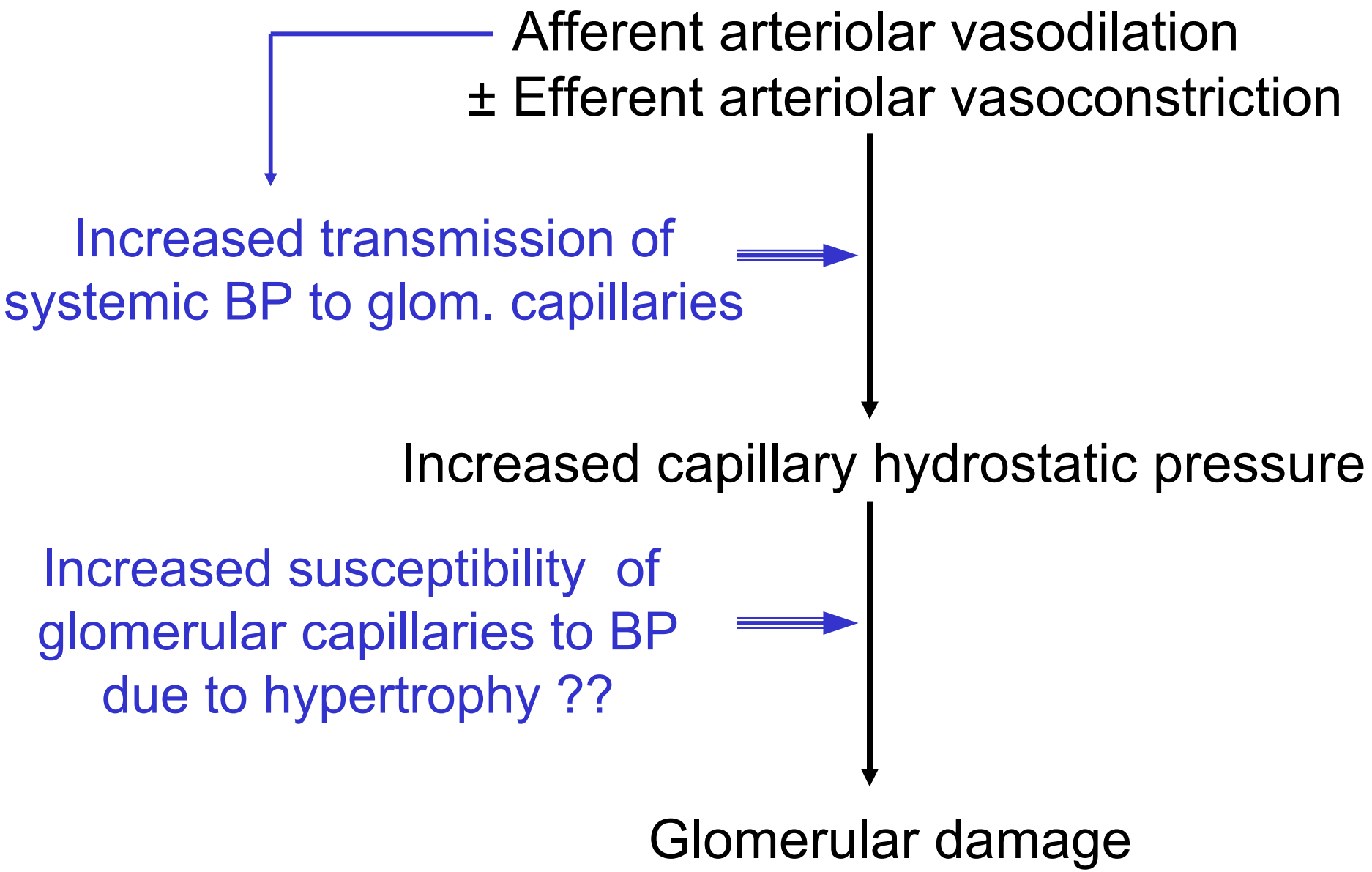
In severe obesity

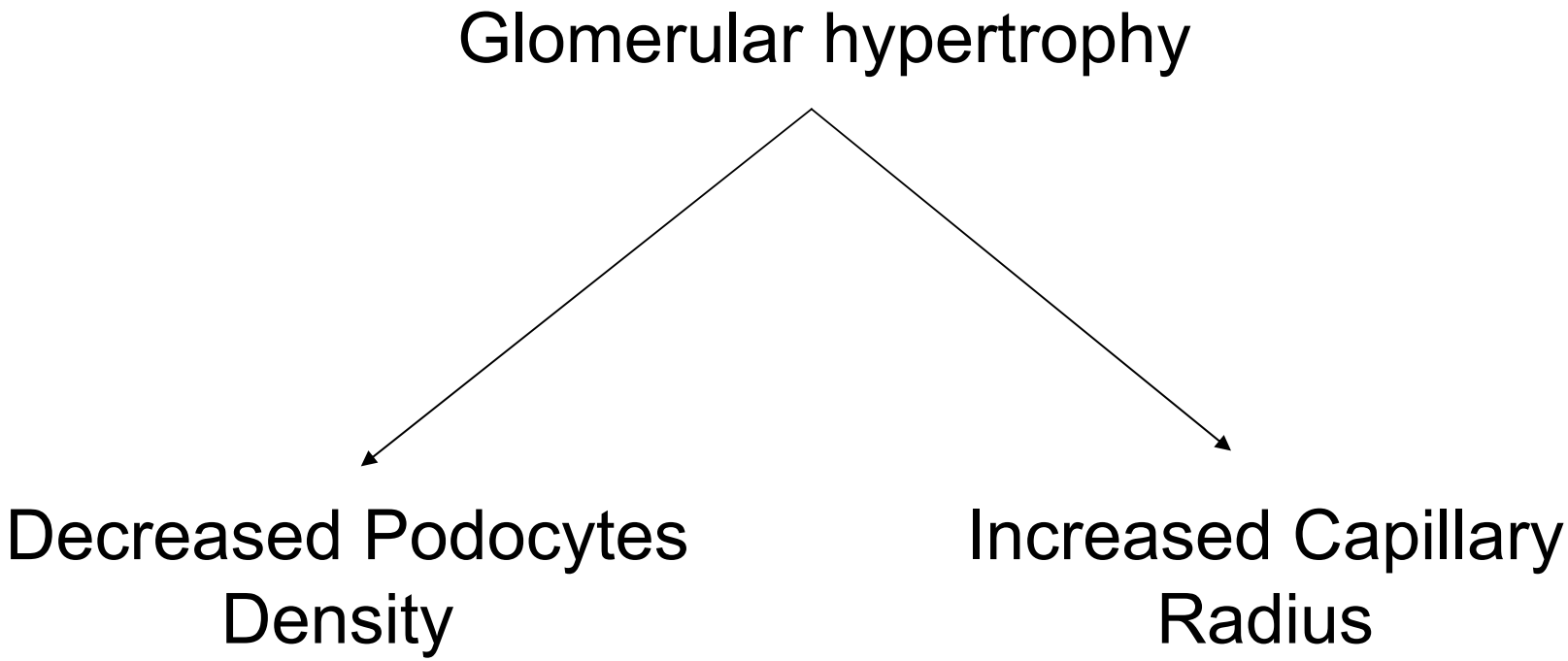
- Increased GFR (+60%)
- Increased RPF (+30%)
- Increased filtration fraction (+25%)

Afferent arteriolar vasodilation
± Efferent arteriolar vasoconstriction

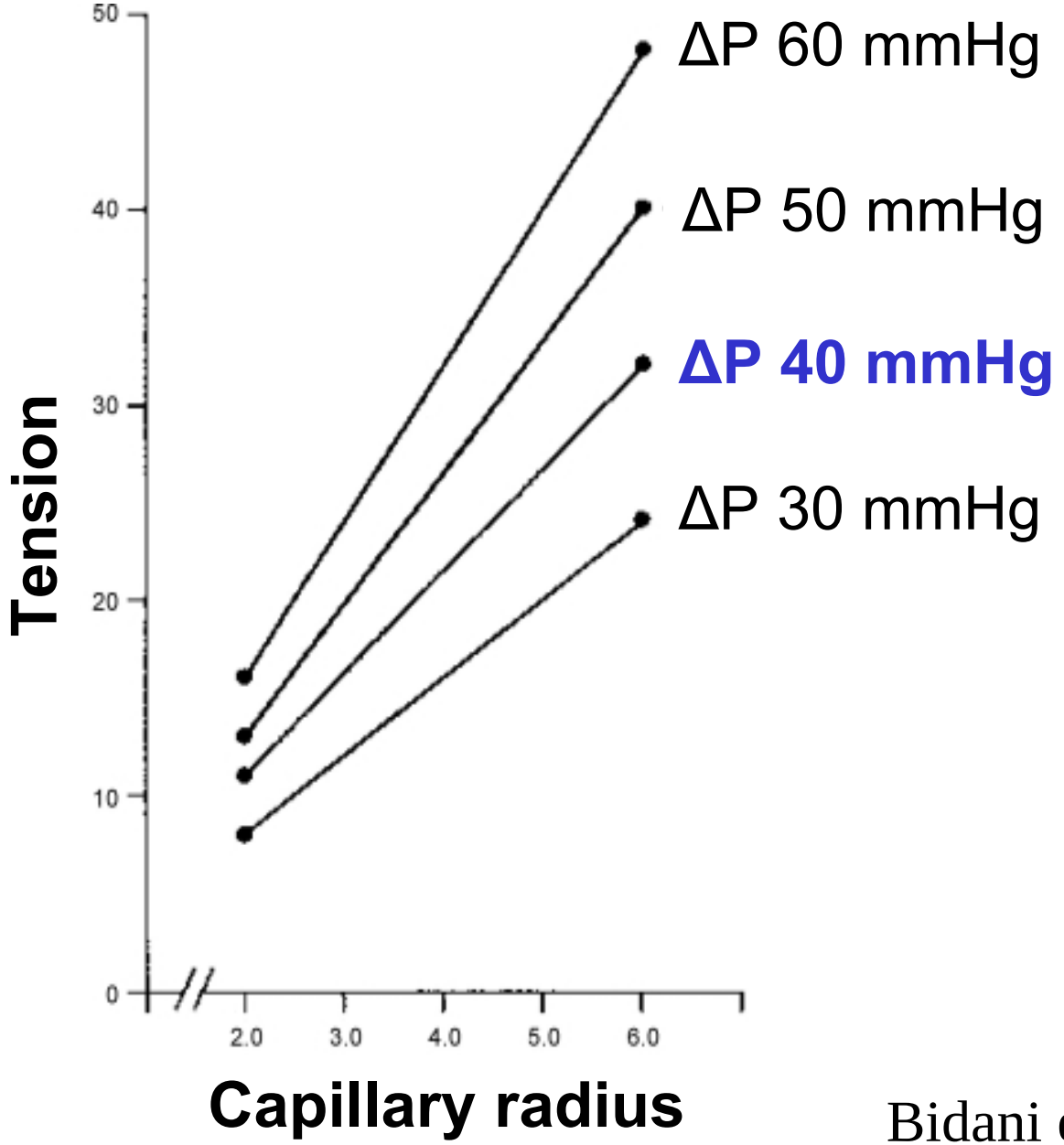
Increased transcapillary hydrostatic pressure


Afferent arteriolar vasodilation
± Efferent arteriolar vasoconstriction
Increased transmission of
systemic BP to glom. capillaries
Increased capillary hydrostatic pressure


Afferent arteriolar vasodilation
± Efferent arteriolar vasoconstriction
Increased transmission of systemic BP to glom. capillaries
Increased capillary hydrostatic pressure
Increased susceptibility of glomerular capillaries to BP due to hypertrophy ??
Glomerular damage


Glomerular hypertrophy
Decreased Podocytes Density
Increased Capillary Radius

Laplace law: Tension = pressure x radius



Bidani et al KI 1990

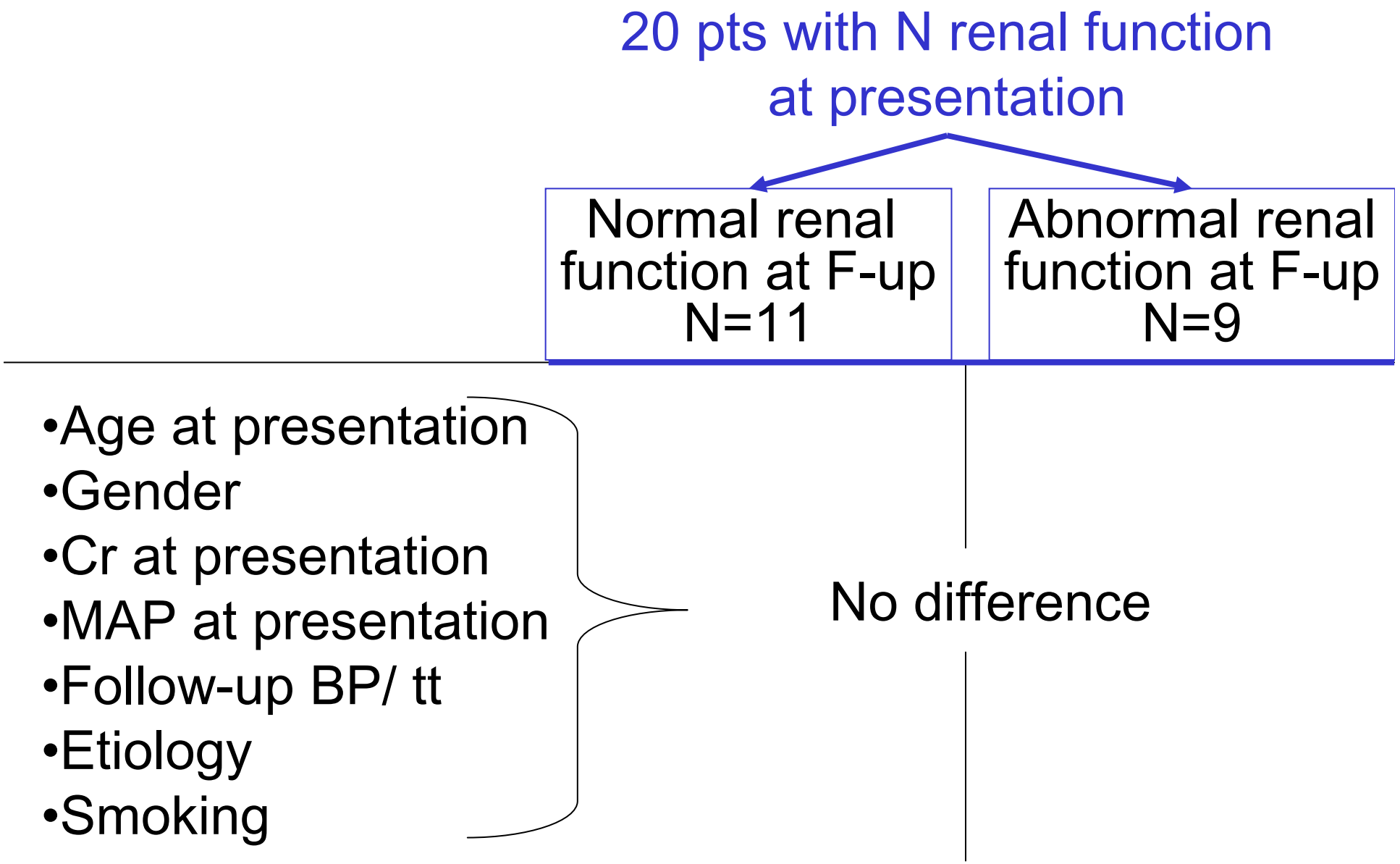
Progression of renal damage in unilateral renal agenesis and in remnant kidney
Gonzalez…Praga: Kidney Int, 2005

54 pts:

- 33 pts with unilateral renal agenesis (URA)
- 21 pts with remnant kidney (RK)
  (1 kidney absent or nonfunctioning
  + lesions in ≥ 50% of remnant kidney)
- Follow up 2-24 yrs (mean 8.3 yrs)

20/54 had N renal function at presentation
(= N Scr and no proteinuria)

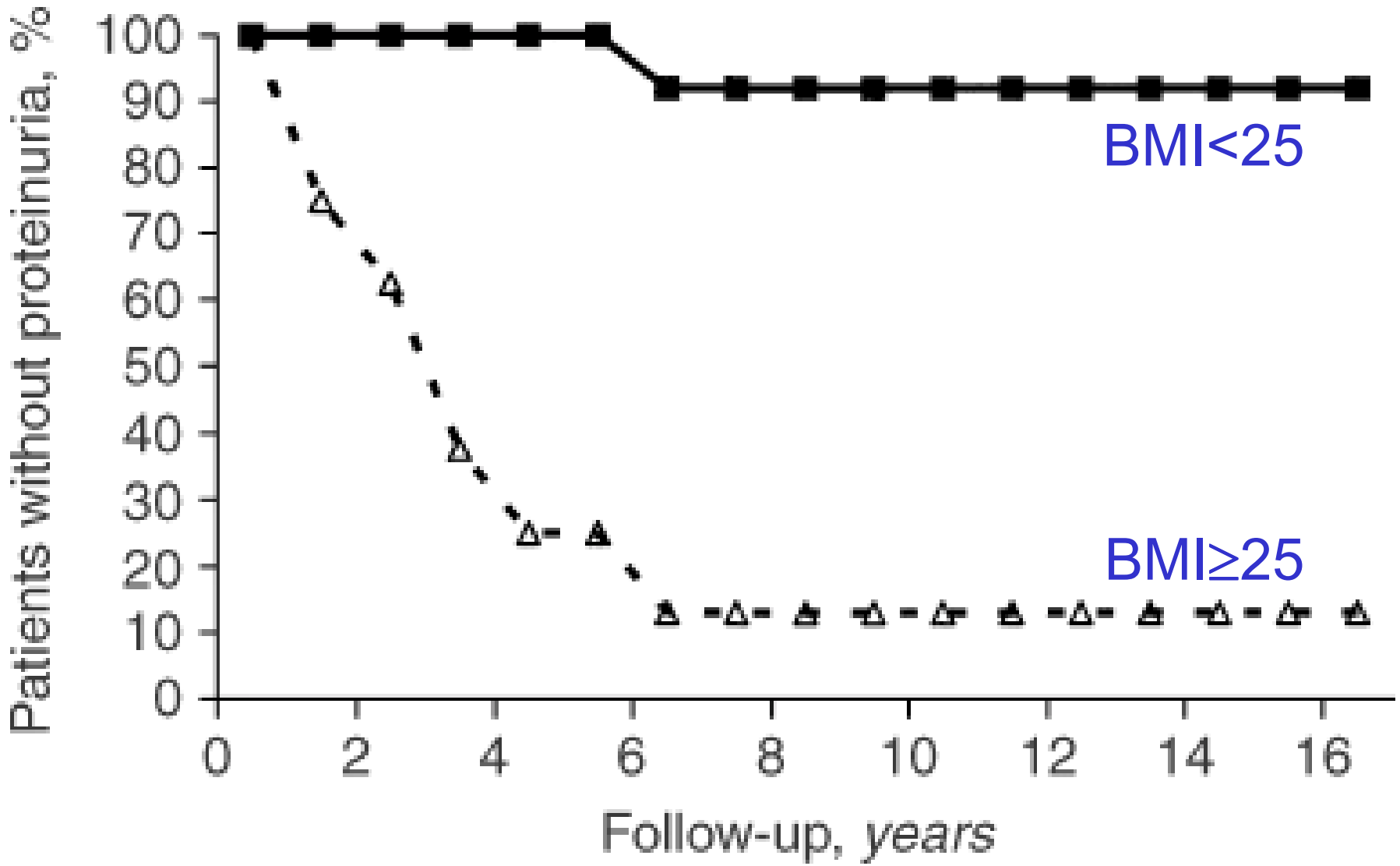
Progression of renal damage / remnant kidney
Gonzalez…Praga: Kidney Int, 2005



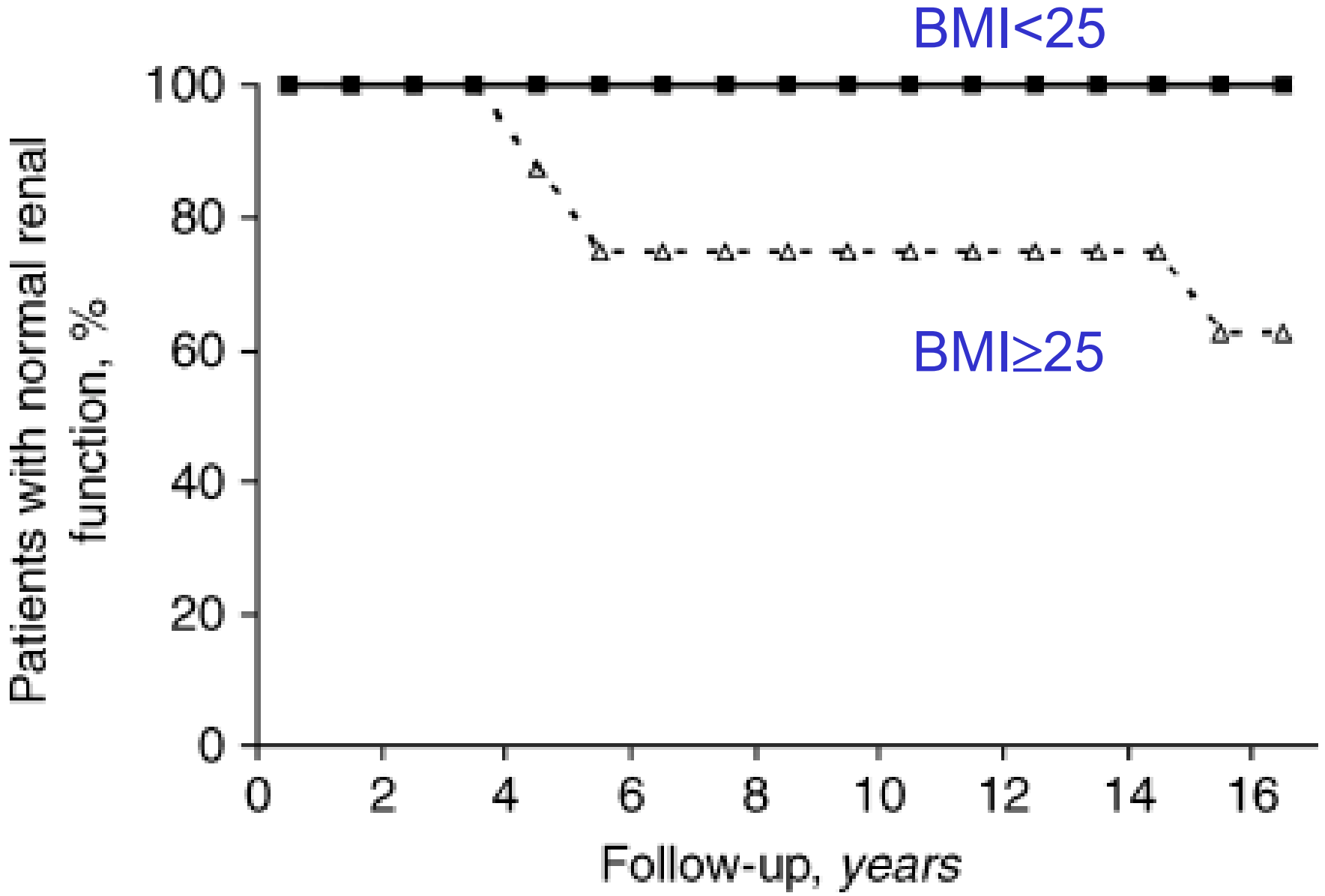
Progression of renal damage / remnant kidney
Gonzalez…Praga: Kidney Int, 2005

20 pts with N renal function at presentation

	Normal renal function at F-up N=11		Abnormal renal function at F-up N=9
•BMI at presentation	21.6±2.6	*	27±3.6
•BMI<25	10/11	*	1/9
•BMI 25- 29.9	1/11	*	3/9
•BMI>30	0/11	*	5/9



Gonzalez…Praga: Kidney Int, 2005



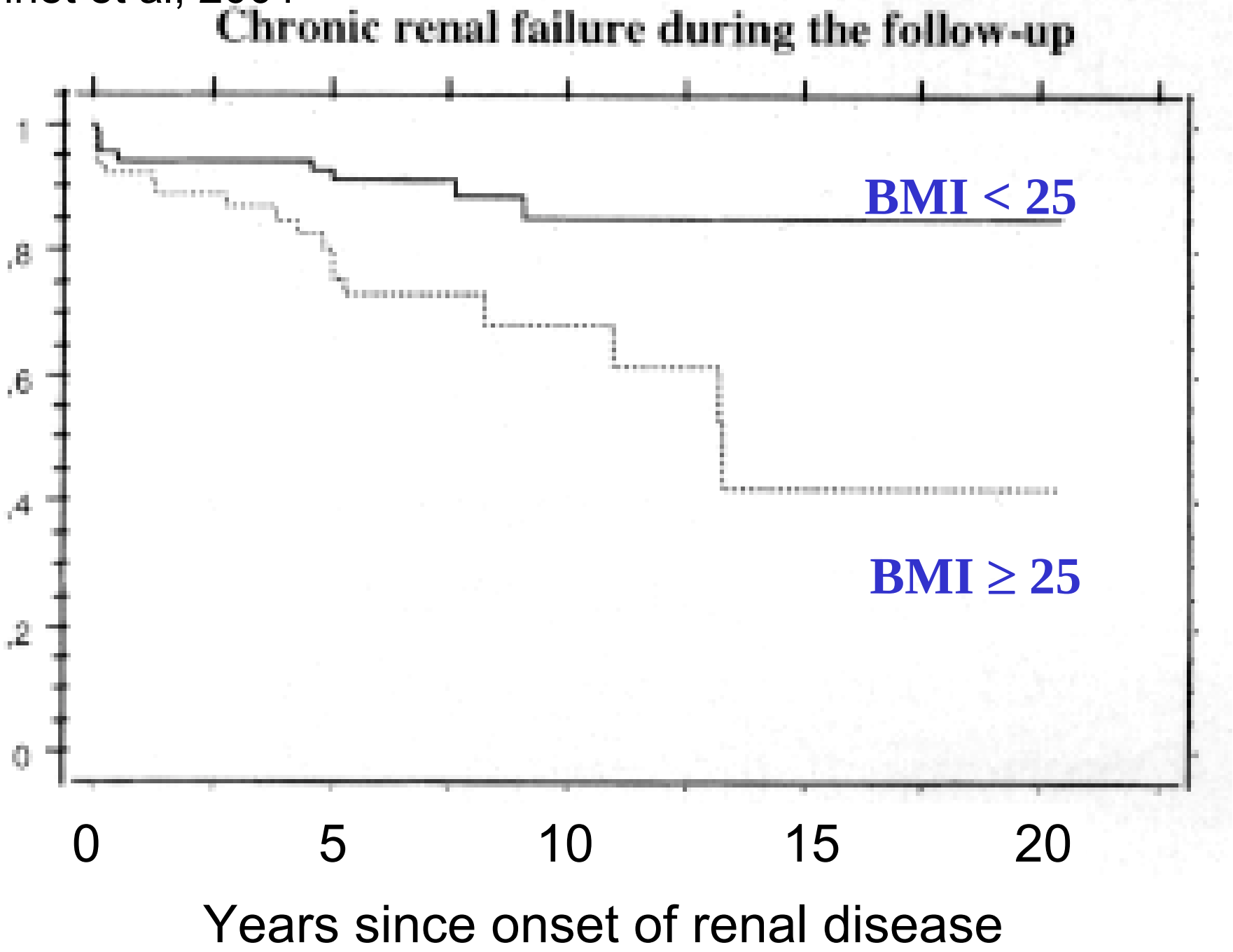
Gonzalez…Praga: Kidney Int, 2005

Increased BMI and progression of IgA nephropathy. Bonnet et al Am J Kidney Dis 2001

162 consecutive cases of IgA nephropathy

At Baseline	BMI≥25	BMI<25
N	67	95
BMI	28.4	22.4
Gender (% men)	74	62
Age	46	36
Proteinuria (g/d)	0.34(0-7)	0.19(0-5)*
%>1g prot/d	33	20*
BP (%HTN)	26	13*
Scr	1.3 ±0.6	1.1 ±0.6
%CRF	21	7*

Bonnet et al, 2001



Increased BMI and progression of IgA nephropathy. Bonnet et al Am J Kidney Dis 2001

Risk factors at baseline for CRF at follow up

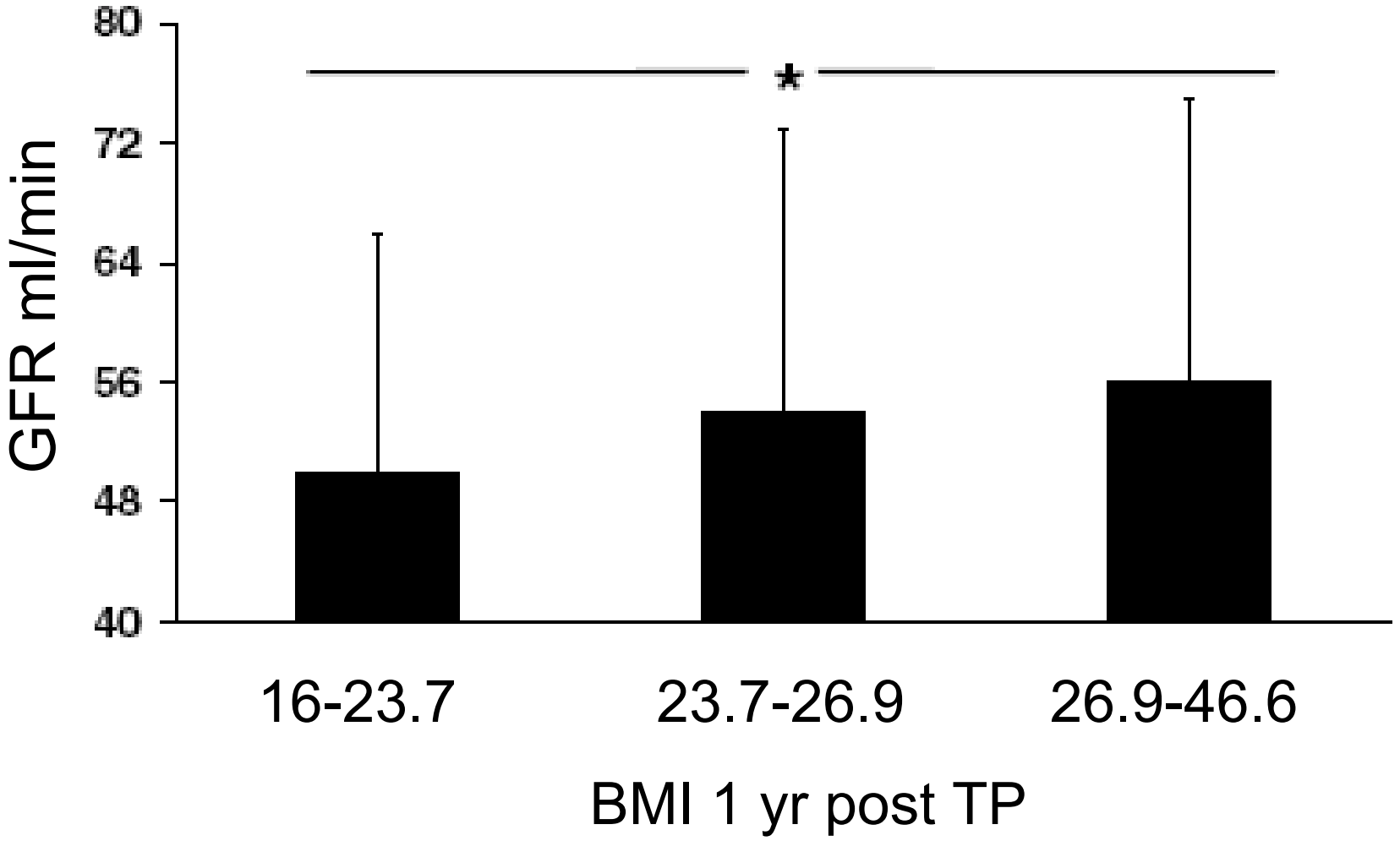
- By univariate analysis:
  - BP
  - Proteinuria>1g/d
  - Histo score
  - BMI
  - Dyslipidemia

- By multivariate (independent):
  - BMI
  - Bordeline: BP; Histo score

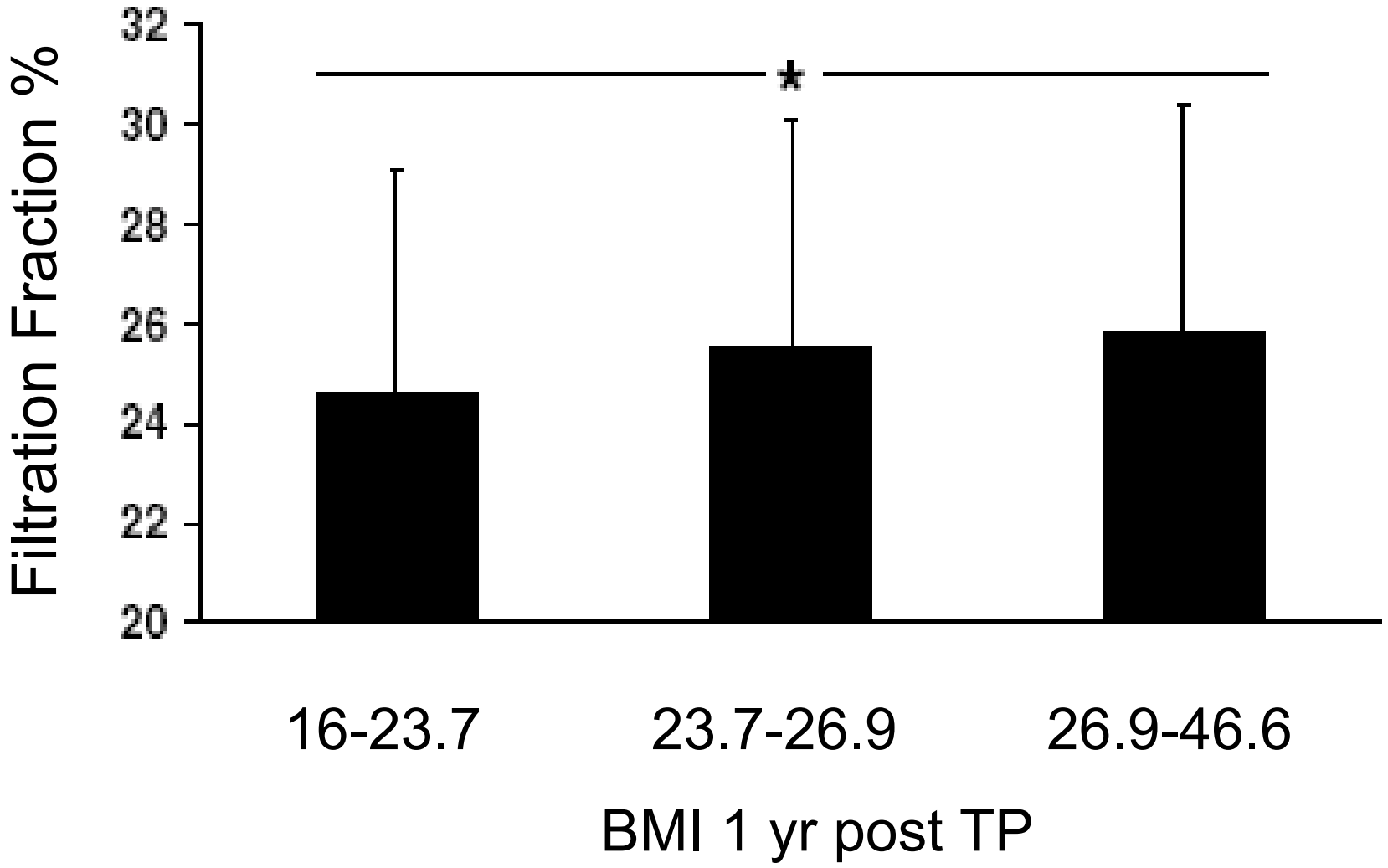
BMI & Glomerular Hyperfiltration in Renal Transplant Recipients. Bosma…Navis, Am J Transplant 2007

- 838 renal transplant recipients
- 1 year post transplant
- Long term follow up

BMI & Glomerular Hyperfiltration in Renal Transplant Recipients. Bosma…Navis, Am J Transplant 2007



BMI & Glomerular Hyperfiltration in Renal Transplant Recipients. Bosma…Navis, Am J Transplant 2007



BMI & Glomerular Hyperfiltration in Renal Transplant Recipients. Bosma…Navis, Am J Transplant 2007

High BMI
High filtration fraction

} At 1 year

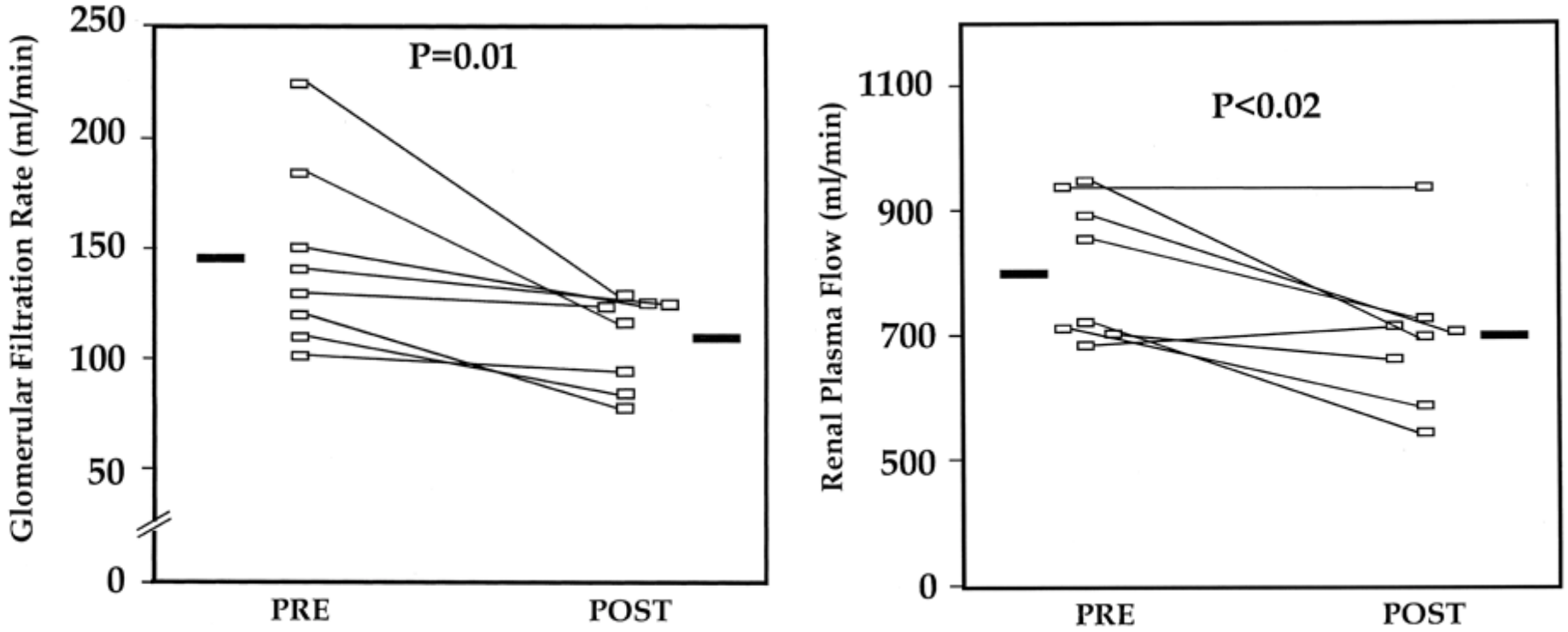
= independent predictors of graft loss

Low renal mass and overweight / obesity have synergistic effects on the kidney

Demonstrated for	•Renal agenesis •Nephrectomy ≥ 50% •Ig A nephropathy •Transplant recipients
To be demonstrated for	•Living kidney donors •Low birth weight •Any kidney disease

How should we manage obese patients with kidney disease?

- Decrease blood pressure (First with ACEI/ARB)
- Put them on a weight reduction diet ???



Chagnac et al, 2003

Weight loss in proteinuric nephropathy
Morales, Praga: Am J Kidney Dis 2003

- Pts with CRF, proteinuria > 1g and BMI>27
- Prospective randomized study
- ACEI/ARB discontinued 2 months prior to randomization
- The effects of a low calorie diet on
    - proteinuria
    - S cr

Weight loss in proteinuric nephropathy
Morales, Praga: Am J Kidney Dis 2003

Low-caloric diet vs Usual diet
= usual diet cal – 500 cal
25-30% fat
55-60% carbohydrate
1-1.2 g/kg/d protein

5 months

Weight loss in proteinuric nephropathy
Morales, Praga. Am J Kidney Dis 2003

	Diet group N=20	Control group N=10
Age	57 (17-74)	56 (34-68)
BMI	33 (28-42)	34 (28-48)
Syst BP	140	135
Diast BP	80	83
S creat (mg/dl)	1.5 (0.7-3.2)	1.6 (1-2.7)
LDL chol (mg/dl)	142	133
Proteinuria (g/d)	2.8 (1-6.6)	3.0 (1-7.8)
Urine Na (mEq/d)	210 (124-324)	192 (54-364)
Urine Urea (g/d)	33	31

Weight loss in proteinuric nephropathy
Morales, Praga. Am J Kidney Dis 2003

	Months	0	1	5
Control group	Δ BW		+0.4	+1.9*
	BMI	34.3	34.5	35.0*
	Proteinuria	3	3.1	3.5
	Scr	1.6	≅	≅

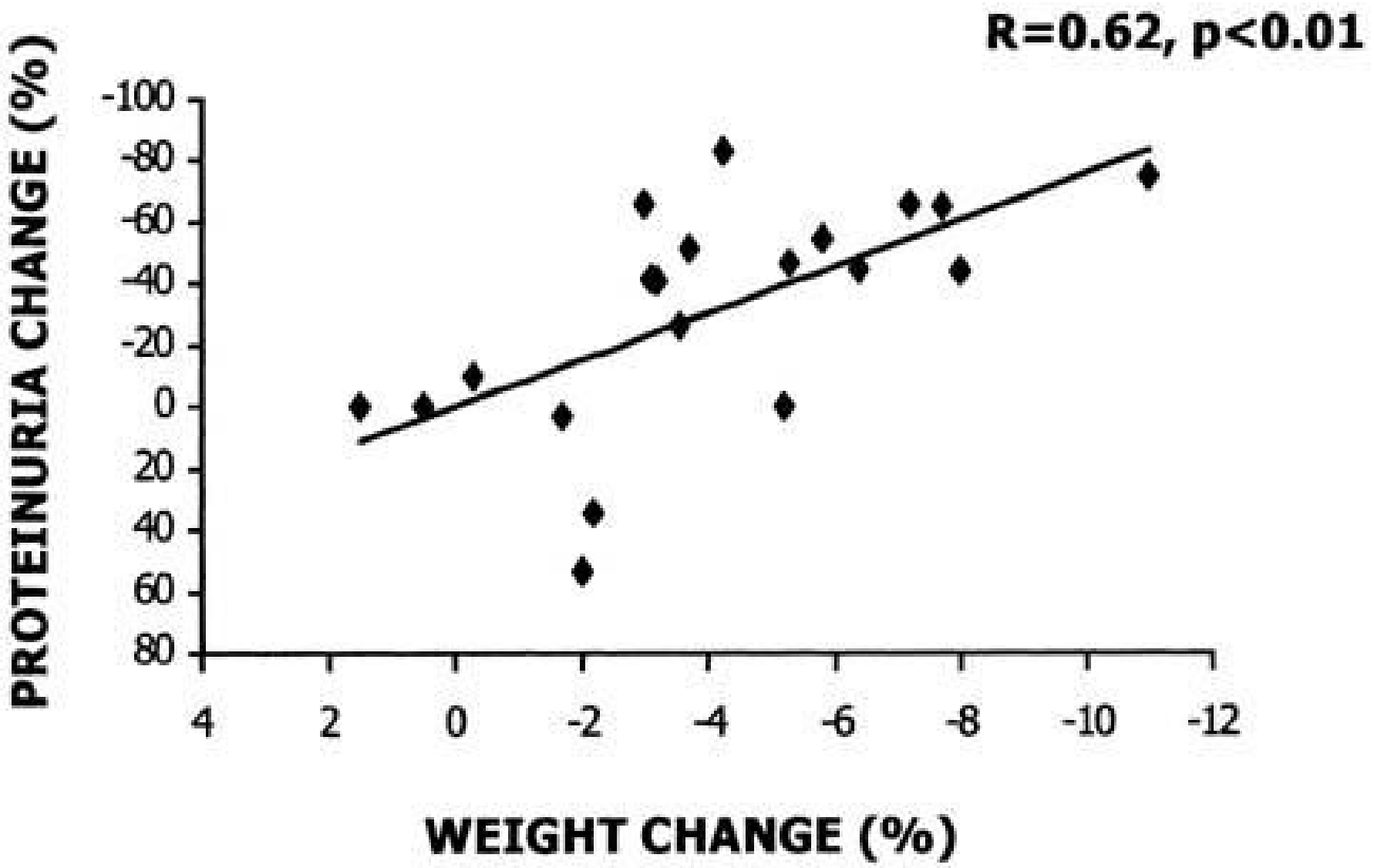
Weight loss in proteinuric nephropathy
Morales, Praga. Am J Kidney Dis 2003

	Months	0	1	5
Control group	Δ BW		+0.4	+1.9*
	BMI	34.3	34.5	35.0*
	Proteinuria	3	3.1	3.5
	Scr	1.6	≅	≅
Diet group	Δ BW		-2.0*	-3.6*
	BMI	33	32.2*	31.6*
	Proteinuria	2.8	2.0*	1.9*
	Scr	1.5	≅	≅

-32%

No change in BP, protein and salt intake in either group

Weight loss in proteinuric nephropathy
Morales, Praga. Am J Kidney Dis 2003



- Weight loss decreases proteinuria in obese patients

- Controlled studies are needed to confirm that weight loss delays the progression of CKD

- Weight loss should be an integral part of the prevention and management of patients with kidney disease and overweight / obesity