Nephropathy and chronic kidney disease in patients with diabetes - characteristics and prognostic implications

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### Overview of the presentation

- 1. Consequences of diabetic nephropathy and chronic kidney disease (CKD) in diabetes
- 2. Tools to screen for incipient or overt diabetic nephropathy
- 3. Formulas to estimate glomerular filtration rate (eGFR)
- 4. How do we define CKD (stages)
- 5. Prevalence of CKD
- 6. Clinical implications of CKD in clinical practice
- 7. Diabetic nephropathy treatment
- 8. Take home messages

1. Consequences of diabetic nephropathy and CKD in patients with diabetes?

### Diabetic nephropathy and mortality in patients with type 1 diabetes



#### CVD MORTALITY IN PATIENTS WITH TYPE 1 DIABETES



#### CANCER MORTALITY IN PATIENTS WITH TYPE 1 DIABETES



## Cox adjusted survival stratified for presence and severity of albuminuria



Groop et al. Diabetes 58, 1651-8, 2009

### Cox adjusted survival stratified for presence and severity of eGFR



### Effect of proteinuria on mortality in Pima Indians with type 2 diabetes



• 97 % of the excess mortality is associated with overt proteinuria

Nelson et al. Diabetes 1988

## CKD is the major predictor of mortality in type 2 diabetes



Population-based study of 1,565 individuals with known type 2 diabetes who were resident in the town of Casale Monferrato in north-west Italy in 1988. There were 670 deaths during 10,780 person years of follow-up

Bruno et al. Diabetologia 2007, 50, 941-948

## CKD is also major predictor of cardiovascular disease



Go et al. NEJM 351, 1296-130, 2004

### Primary causes of kidney failure over time (RRT)



USRDS, 2004



### The Added Burden of CKD

### 2. Tools to screen for incipient or overt diabetic nephropathy

### Screening for microalbuminuria



### Definitions of albuminuria

*Normoalbuminuria: a* timed overnight urinary albumin excretion rate (AER) <20  $\mu$ g/min or <30 mg/24 h or an albumin-creatinine ratio (ACR) of <2.5 mg/mmol for men and <3.5 for women in a first morning urine sample

*Microalbuminuria*: AER 20-200 µg/min or 30-300 mg/24 h or an ACR of 2.5-25 mg/mmol for men and 3.5-35 for women in a first morning urine sample

Macroalbuminuria: AER >200  $\mu$ g/min or >300 mg/24 h or an ACR of >25 mg/mmol for men and >35 for women in a first morning urine sample



Type 1 diabetes

Microalbuminuria type 2 diabetes

NEAR NORMAL HISTOLOGY (C1) - 30 %



(a) Both normal and totally destroyed glomeruli

(b) Severe arterioliohyalinosis



NON-SPECIFIC FINDINGS (C3) - 40 %





TYPICAL DIABETIC

(c) Tubulointerstitial fibrosis



Fioretto et al. Diabetologia 1998;41:233-236

## Change in GFR (%) in patients with type 2 diabetes and microalbuminuria

(n=33, 4 year follow-up)



Nosadini et al. Diabetes 2000;49:476-484

# 3. Formulas to estimate glomerular filtration rate (eGFR)

### Estimation of renal function

Renal function can be estimated using the *Cockcroft-Gault formula*, the *MDRD-4 formula* or the *CKD-EPI equation* 

The *Cockroft-Gault formula* provides an estimate of the creatinine clearance (eCCr)

eCCr= [(140-age) x body weight (kg) x constant (1.23 for men and 1.04 for women)]/serum creatinine (mmol/l)

The data has to be adjusted for a normal body surface area of 1.73  $\ensuremath{\text{m}}^2$ 

Cockcroft and Gault. Nephron 16, 31-41, 1976

### Estimation of renal function

*MDRD-4 formula* provides an estimate of the glomerular filtration rate (eGFR)

 $eGFR = 186 \times serum creatinine (mg/dl)^{-1.154} \times age^{-0.203} \times [1.210 if black] \times [0.742 if woman].$ 

For the use with the new gold standard IDMS-traceable serum creatinine assays, a revised version of the formula should be used.

> Levey et al Ann Intern Med 130, 461-470, 1999 Levey et al Ann Intern Med 145, 247-254, 2006

### Estimation of renal function

The *CKD-EPI equation*, expressed as a single equation:

eGFR-EPI = 141 × min(Scr/κ, 1)α × max(Scr/κ, 1)-1.209 × 0.993Age × 1.018 [if female] \_ 1.159[if black]

Scr = serum creatinine  $\kappa$  is 0.7 for females and 0.9 for males  $\alpha$  is -0.329 for females and -0.411 for males min indicates the minimum of Scr/kor 1 max indicates the maximum of Scr/k or 1

Levey et al Ann Intern Med 150 (9): 604-612, 2009

### 4. How do we define chronic kidney disease (CKD)?

## Stages of renal function are defined as follows (KDOQI)

Stage I - eGFR >90 ml/min + persistent albuminuria

Stage II - eGFR 60-90 ml/min + persistent albuminuria

Stage III - eGFR 30-60 ml/min

Stage IV - eGFR 15-30 ml/min

Stage V - eGFR <15 ml/min

KDOQI Am J Kidn Dis, Vol 49, No 2, Suppl 2 (February), 2007: pp 513-519

### Definition/classification of CKD

"All individuals with a glomerular filtration rate (GFR) <60 ml/min/1.73 m<sup>2</sup> for 3 months are classified as having chronic kidney disease, irrespective of the presence or absence of kidney damage......

NKF (2002). <u>clinical practice guidelines for chronic kidney disease</u>

## 5. Prevalence of chronic kidney disease (CKD)

## Prevalence of CKD in the US based upon the NHANES

 Table 3. Prevalence of Chronic Kidney Disease (CKD) Stages in US Adults Aged 20 Years or Older Based on NHANES 1988-1994 and

 NHANES 1999-2004

01/5	Prevalence, % (95% Cl)		Prevalence Ratio for	Estimated No. of
CKD Stage <sup>a</sup>	NHANES 1988-1994	NHANES 1999-2004	NHANES 1999-2004 to 1988-1994 (95% CI)	US Adults in 2000, No. in Millions (95% Cl)
1	1.71 (1.28-2.18)	1.78 (1.35-2.25)	1.05 (0.85-1.30)	3.6 (2.7-4.5)
2	2.70 (2.17-3.24)	3.24 (2.61-3.88)	1.21 (1.03-1.41)	6.5 (5.2-7.8)
3	5.42 (4.89-5.95)	7.69 (7.02-8.36)	1.42 (1.25-1.62)	15.5 (14.1-16.8)
4	0.21 (0.15-0.27)	0.35 (0.25-0.45)	1.70 (1.11-2.51)	0.7 (0.5-0.9)
5	NA	NA	NA	NA
Total	10.03 (9.16-10.91)	13.07 (12.04-14.10)	1.30 (1.19-1.43)	26.3 (24.2-28.3)

Abbreviations: CI, confidence interval; NA, data not included because patients with CKD stage 5 were excluded; NHANES, National Health and Nutrition Examination Surveys. <sup>a</sup> Defined based on standard criteria<sup>1</sup>: stage 1, persistent albuminuria with glomerular filtration rate (GFR) higher than 90 mL/min/1.73 m<sup>2</sup>; stage 2, persistent albuminuria with GFR of 60 to 89 mL/min/1.73 m<sup>2</sup>; stage 3, GFR of 30 to 59 mL/min/1.73 m<sup>2</sup>; stage 4, GFR of 15 to 29 mL/min/1.73 m<sup>2</sup>. The age-adjusted prevalence rates for CKD stages 1, 2, 3, and 4 in 1988-1994 adjusted to the 1999-2004 age distribution in Table 1 are 1.7%, 2.8%, 5.6%, and 0.2%, respectively, for a total of 10.3%.

Coresh et al. JAMA 2007, 298, 2038-2047

### Prevalence of CKD stage by age

Figure 2. Prevalence of Chronic Kidney Disease (CKD) Stages by Age Group in NHANES 1988-1994 and 1999-2004



NHANES indicates National Health and Nutrition Examination Surveys. <sup>a</sup>There were no cases in 1988-1994.

Coresh et al. JAMA 2007, 298, 2038-2047

## Prevalence of CKD by type of diabetes in Japan

	Type 1 diabetes $(n = 504)$	Type 2 diabetes $(n = 3071)$
ACR (mg/g creatinine) geometric mean (95% CI)	12.9 (11.5-14.6)	29.9 (28.1-31.8)*
Albuminuria (ACR $\geq$ 30 mg/g), $n$ (%)	80 (15.9)	1109 (36.1)*
Microalbuminuria (ACR 30–299 mg/g), $n$ (%)	52 (10.3)	719 (23,4)*
Macroalbuminuria (ACR $\geq$ 300 mg/g), <i>n</i> (%)	28 (5.6)	390 (12.7)*
eGFR (ml/min/1.73 m <sup>2</sup> ), means $\pm$ SD	$86.6 \pm 20.5$	$72.1 \pm 22.4^{*}$
$eGFR < 60 \text{ ml/min}/1.73 \text{ m}^2, n$ (%)	40 (7.9)	775 (25.2)*
Albuminuria and/or eGFR < 60 ml/min/1.73 m <sup>2</sup> , $n$ (%)	96 (19.1)	1416 (46.0)*
Chronic kidney disease stage, $n$ (%)		
1 (ACR $\ge$ 30 mg/g and eGFR $\ge$ 90 ml/min/1.73 m <sup>2</sup> )	23 (4.6)	178 (5.8)
2 (ACR $\ge$ 30 mg/g and eGFR = 60–89 ml/min/1.73 m <sup>2</sup> )	33 (6.5)	460 (15.0)
$3 (eGFR = 30-59 \text{ ml/min}/1.73 \text{ m}^2)$	35 (6.9)	633 (20.6)
4 (eGFR = $15-29 \text{ ml/min}/1.73 \text{ m}^2$ )	5 (1.0)	103 (3.4)
5 (eGFR < 15 ml/min/1.73 m <sup>2</sup> )	0 (0.0)	39 (1.3)

Ohta et al. Diabet. Med. 2010, 27, 1017-1023

### Scatter plots for eGFR against ACR in type 1 and type 2 diabetes



Shaded area denotes CKD defined as ACR ≥30 mg/g and/or eGFR < 60 ml/min/1.73 m<sup>2</sup> Ohta et al. Diabet. Med. 2010, 27, 1017-1023

### Age, gender, race/ethnicity adjusted prevalence of CKD stages 1-4



### What if we measure kidney function and albuminuria at the same time?

The distribution of albuminuria and an eGFR <60 ml/min/1.73 m<sup>2</sup> in patients with T2D in Australia



\* The unshaded area denotes patients without chronic kidney disease (52.9%).

Nephron Study N=3.893 patients with Type 2 diabetes 52% males

#### National Evaluation of the Frequency of Renal impairment coexisting with NIDDM

### CKD in 1 out of 2



The NEFRON study showed that if every patient with type 2 diabetes you saw today had their serum creatinine measured, an automatic report of an eGFR < 60mL/min/1.73m<sup>2</sup> would be returned in:



CKD is common in patients with type 2 diabetes. The NEFRON study showed that if every patient with type 2 diabetes you saw today had their urine tested:



6. What are the implications for clinical practice?

## Finding an eGFR <60 means that your patient....

- is at high risk of a heart attack or stroke
- is less likely to survive a heart attack
- is likely to be hospitalized within the next 12 months
- has heart failure (diagnosed or undiagnosed)
- will have problems with wound healing
- has problems to control ankle swelling and fluid retention
- blood pressure targets are more difficult to achieve
- is likely to get a hip fracture if he/she falls over
- while glucose levels may be easier to control vigilance may be warranted to avoid hypoglycemia

Table 2. Recommendations for Non-Insulin Hyperglycem	ia Drug Therapy for Patients With Moderate to Severe CKD

Class	Drug	CKD Stage 3–5	Dialysis	Complication
First-generation	Acetohexamide	Avoid	Avoid	Hypoglycemia
sulfonylurea	Chlorpropamide	GFR 50–70 ml/min/1.73 m <sup>2</sup> : ↓ 50% GFR < 50 ml/min/1.73 m <sup>2</sup> : Avoid	Avoid	Hypoglycemia
	Tolazamide	Avoid	Avoid	Hypoglycemia
	Tolbutamide	Avoid	Avoid	Hypoglycemia
Second-generation	Glipizide	No dece adjustment	No dose adjustment	
sulfonylurea	Glyburide	Avoid	Avoid	Hypoglycemia
	Glimephice	Low dose: 1 mg/day	Avoid	Hypoglycemia
$\alpha$ -Glucosidase inhibitors	Acarbose	SCr > 2 mg/dl: Avoid	Avoid	Possible hepatic toxicity
	Miglitol	$SCr \ge 2 \text{ mg/dl}$ : Avoid	Avoid	
Biguanide	Metformin	Contraindicated: Male: SCr > 1.5 mg/dl Female: SCr > 1.4 mg/dl	Avoid	Lactic acidosis
TZDs	Pioglitazone	No dose adjustment	No dose adjustment	Volume retention
	Rosiglitazone	No dose adjustment	No dose adjustment	Volume retention
Meglitinides	Repaglinide	No dose adjustment	No dose adjustment	
	Nateglinide	Initiate low dose: 60 mg	Avoid	Hypoglycemia
Incretin mimetic	Exenatide	No dose adjustment	No dose adjustment	
Amylin analog	Pramlintide	No dose adjustment GFR + 29 ml/min/1 72 m <sup>2</sup> : Unknown	Unknown	
Dipeptidyl-peptidase I inhibitor	Sitagliptin	GFR 30–50 ml/min/1.73 m <sup>2</sup> : ↓ 25% GFR < 30 ml/min/1.73 m <sup>2</sup> : ↓ 50%	↓ 50%	Hypoglycemia

Cavanaugh. Clinical Diabetes 25, (3) 2007

### Sulphonylurea use in Australia



### Metformin use in Australia

The use of metformin is specifically cautioned in patients with impaired kidney function



Thomas et al. The Nephron Study



### So what was the problem?

### SCREENING FAILURE!

A positive screening demands intervention

DIAGNOSTIC TESTING

· CHANGE IN MANAGEMENT

THERE IS NO VALIDITY IN SCREENING FOR RISK OR DISEASE IF IT'S RESULTS DON'T LEAD TO ACTION!

### 7. Diabetic nephropathy treatment



### Treament of diabetic nephropathy

- Try to achieve optimal glucose control
  - HbA1c target <7%
- Stop smoking
- Lowering of blood pressure
  - RR target < 130/80
  - RR target < 120/75 if proteinuric (of 1 g)
- Use ACE-inhibitors and/or AR blockers
- Consider lipid-lowering treatment

### 8. Take home messages

CKD is a serious complication

 CKD is present in 1 out of 2 patients with type 2 diabetes

 We should screen for CKD on a regular basis

If CKD is diagnosed it is a call for action



Finding an eGFR < 60 mL/min/1.73m<sup>2</sup> in your patient really means:

### You have an opportunity to make a difference to your patient's care



### IT WOULD NEVER HAPPEN TODAY!

## Thank you for your attention

and the second second