Non-proteinuric pathways in loss of renal function in patients with type 2 diabetes
Diabetic Nephropathy

**Syndrome characterized by:**
- macro-albuminuria
- declining renal function
- and increased cardiovascular mortality
Diabetic Nephropathy - Temporal perspective

Graph showing the progression of GFR (mL/min) over time with different stages of albuminuria:
- **Normoalbuminuria**
- **Microalbuminuria**
- **Proteinuria**
Is there another pathway of renal function loss in diabetes?
During the last decade, several studies observed that patients with T2DM may have reduced renal function (GFR <60 ml/min) or advanced renal disease (GFR <30ml/min) in the absence of proteinuria.
Non-proteinuric GFR decline

- > 12 studies
  - Cross sectional studies
  - Cohort studies
  - Decline studies (measured GFR)
1197 patients; 171 (13%) had < 60ml/min (2003)

- **36% normoalbuminuria**
- **45% microalbuminuria**
- **19% macroalbuminuria**

2798 patients; 575 (21%) had < 60ml/min (2013)

- **52% normoalbuminuria**
- **48% microalbuminuria, macroalbuminuria**

*Krammer H et al, JAMA 2003; Mottl A. J Diabetes Complications. 2013*
RIACE study 2012-

- 15733 patients; 2959 (19%) with <60ml/min.
  - 57 % normoalbuminuria
  - 31 % microalbuminuria
  - 12 % macroalbuminuria

- 258 (2 %) with <30ml/min
  - 26 % normoalbuminurial
  - 34 % microalbuminuria
  - 40 % macroalbuminuria

Solini G. et al, Diabetes Care 2012.
Non-proteinuric GFR decline

- Evidence
  - Prospective studies
4006 patients with normoalbuminuria and GFR > 60 ml/min.
Follow up: 15 years.

- 575 (14%) only developed GFR < 60 ml/min
- 977 (24%) only developed microalbuminuria-proteinuria
- 557 (14%) developed both conditions

- reduced GFR preceded micro- in 16% of the cases.
Swedish National Diabetes Registry (NDR) *

- 3667 patients (with normoalbuminuria and no CKD)
- Follow-up: 5 years.

- 290 (8%) only developed GFR < 60 ml/min
- 612 (17%) only developed microalbuminuria-proteinuria
- 117 (3%) developed both conditions

- Incidence of non-proteinuric CKD: 6-7% per year.

Afghahi H et al NDT 2010
Microalbuminuria and macroalbuminuria do not always precede loss of renal function in type 2 diabetes...
Non-proteinuric GFR decline

- Evidence
  - Decline studies
The BENEDICT and DEMAND cohorts

- 600 subjects with type 2 diabetes
- Normo- microalbuminuria
- Hypertension
- Normal or supra-normal renal function
- Treatment: BP < 120/80 mmHg; HbA1c <7%

- Measured GFR (iohexol) every 6 months (mean 4 y)
- Outcome: GFR decline over time

Ruggenenti P et al Diabetes Care 2013
GFR decline: 3.37 (5.26–1.64)
### The BENEDICT and DEMAND cohorts

<table>
<thead>
<tr>
<th></th>
<th>GFR decline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>3.37 (5.57-1.31)</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>2.66 (5.03-1.16)</td>
</tr>
<tr>
<td>Normoalbuminuria</td>
<td>3.50 (5.69-1.42)</td>
</tr>
</tbody>
</table>

*ACEi* yes: 3.31 (5.33-1.31)

*ACEi* no: 3.53 (5.77-1.44)

*p* value 0.139

*p* value 0.663

*Ruggenenti P et al Diabetes Care 2013*
Non-proteinuric vs proteinuric GFR decline

1 ml/min
(the general population)

3.37 (5.26–1.64) ml/min
(normo-microalbuminuria-BENEDICT-DEMAND)

5.2 ± 4.1 ml/min
(726 mg/24 ; gm, 95% CI: 122- 4319; STENO study)

10.08 ± 2.52 ml/min
(~3 gr/24 h, REIN study)
Non-proteinuric GFR decline

- Pathogenesis
Pathogenesis

- Gender differences

- Metabolic Syndrome risk factors
  - Obesity
  - Hypertension
  - Lipids
  - Subclinical inflammation
  - Others

- Glomerular hyperfiltration
Gender differences

- UKPDS study
  - *Male gender* was a risk factor for albuminuria: HR: 1.47
  - *Female gender* was a risk factor for CKD: HR 1.45.

- NDR study
  - *Female gender* was a protective factor for albuminuria, OR: 0.65
  - *Female gender* was a risk factor for CKD, OR 4.03.
In non diabetic patients, women are protected for accelerated GFR decline
Effect of Gender on the Progression of Nondiabetic Renal Disease: A Meta-Analysis

JOEL NEUGARTEN, ANJALI ACHARYA, and SHARON R. SILBIGER
Renal Division, Department of Medicine, Montefiore Medical Center and the Albert Einstein College of Medicine, Bronx, New York.

- Chronic nephropathies, IgA, GNM, PQR.

- GFR progression is faster in men than in women.
GFR decline in living donors (men and women)

8.7 ml/min per decade. 1.4 ml/min per decade.
Gender differences

- It seems that this benefit is lost in diabetes.
Pathogenesis

- Metabolic Syndrome risk factors
  - Obesity
  - Hypertension
  - Lipids
  - Subclinical inflammation
  - Others
## Metabolic Syndrome

<table>
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<tr>
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<th>Risk for non proteinuric CKD</th>
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<tbody>
<tr>
<td>Overweight (25-30 BMI)</td>
<td>1.53 (1.10-3.14)</td>
</tr>
<tr>
<td>Obesity (30-35 BMI)</td>
<td>1.90 (1.33-2.70)</td>
</tr>
<tr>
<td>Prominent Obesity (&gt;35)</td>
<td>2.26 (1.47-3.48)</td>
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Afghahi H et al NDT 2010
Metabolic Syndrome

- Triglyceride levels
- Systolic blood pressure

NDR and UKPDS studies
## Gender differences in metabolic traits in diabetes

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<tr>
<td>Lipid accumulation</td>
<td>central</td>
<td>Peripheral (changes to central after menopause)</td>
</tr>
<tr>
<td>Inflammation</td>
<td>++</td>
<td>++++</td>
</tr>
<tr>
<td>Post-load glucose levels</td>
<td>++</td>
<td>++++</td>
</tr>
<tr>
<td>Lipid profile TG; HDL col</td>
<td>++</td>
<td>++++</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>++</td>
<td>++++</td>
</tr>
<tr>
<td>CV risk profile</td>
<td>++</td>
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In the non-proteinuric phenotype the prevalence of diabetic retinopathy is low.

RIACE study: > 15000 patients.

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<th>&lt; 60 ml/min + normoalbuminuria</th>
<th>&lt; 60 ml/min + microalbuminuria or macroalbuminuria</th>
<th>p</th>
</tr>
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<tr>
<td>Advanced Retinopathy</td>
<td>10.5%</td>
<td>22.4%</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Renal disease in T2DM is more heterogeneous than in T1DM.

About 30% of the subjects with microalbuminuria can show either:
- mild histological changes
- classic diabetic nephropathy
- atypical patterns of renal injury

Fioretti P. et al. Diabetologia. 1996
Renin-angiotensin-aldosterone system.

ACE-I or ARB the incidence of:
- renal events (2-fold increase of serum creatinine, ESRD or death); Brenner et al. *NEJM* 2001.
- macroalbuminuria
- microalbuminuria; the BENEDICT trial
## The BENEDICT and DEMAND cohorts

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*Ruggenenti P et al Diabetes Care 2013*
ACE-inhibitors

- 285 subjects with T1DM,
- normoalbuminuria and normal BP.
- randomized to enalapril, losartan or placebo
- patients underwent repeated renal biopsies and measured GFR.

Mauer M et al NEJM. 2009
the change in mesangial fractional volume per glomerulus was similar in all groups.

the decrease of GFR over time was similar between groups
Non-proteinuric GFR decline

- 30-50% of patients with T2DM and CKD have normo- or microalbuminuria.
- Particularly frequent in women.
- Accelerated GFR decline (3ml/min/y)
- Independent of normo/microalbuminuria
- Retinopathy in infrequent.
- Independent of ACE-inhibitors?
Conclusions

- Two different phenotypes
  - Proteinuric ("classic diabetic nephropathy")
  - Non-proteinuric GFR decline
Non-proteinuric pathways in loss of renal function in patients with type 2 diabetes

Esteban Porrini, Piero Ruggenenti, Carl Erik Mogensen, Drazenka Pongrac Barlovic, Manuel Praga, Josep M Cruzado, Radovan Hojs, Manuela Abbate, Aiko P J de Vries, for the ERA-EDTA diabetes working group.
Pathways

T2DM → CKD → ESRD

Normoalbuminuria - Microalbuminuria - Macroalbuminuria

Normoalbuminuria - Microalbuminuria

CARDIOVASCULAR DISEASE
Non-proteinuric GFR decline

- If a man will begin with certainties, he shall end in doubt; but if he will be content to begin with doubts, he shall end in certainties.

Francis Bacon
DIABESITY: Diabetes and Obesity in Renal Disease

Tenerife, November 1 and 2, 2014

CME course of the DIABESITY WORKING GROUP of the ERA-EDTA

Carl Erik Mogensen
Manuela Abbate
Vivette D'Agati
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Josep Cruzado
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Piero Ruggenenti
Eduardo Salido
Aiko De Vries
Ana Wagner
Ruan Xiong-Zhong
Glomerular Hyperfiltration
Long-term GFR decline (ml/min/1.73m² per year)

month 6 to study end

p=0.010
The reduction of hyperfiltration protects from this non albuminuric accelerated GFR decline:

- **Persistent HF**: 5 ml/min/year
- **Ameliorated HF**: 2 ml/min/year
About 382 million people have type 2 diabetes (T2DM)

592 million will have T2DM by 2035.

T2DM is a major cause of CKD

- ~30% of ESRD (Europe and Canada)
- ~50% of ESRD (USA)
### Table 4. OR of developing CKD over 9 years of follow-up by quintile of HOMA-insulin resistance

<table>
<thead>
<tr>
<th>HOMA-Insulin Resistance Quintile</th>
<th>Multivariable-Adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quintile 1 (&lt;1.2)</td>
<td>1.00 (Referent)</td>
</tr>
<tr>
<td>Quintile 2 (1.2 to 1.7)</td>
<td>1.17 (0.88 to 1.54)</td>
</tr>
<tr>
<td>Quintile 3 (1.8 to 2.4)</td>
<td>1.42 (1.08 to 1.87)</td>
</tr>
<tr>
<td>Quintile 4 (2.5 to 3.6)</td>
<td>1.35 (1.02 to 1.80)</td>
</tr>
<tr>
<td>Quintile 5 (≥3.6)</td>
<td>1.70 (1.26 to 2.30)</td>
</tr>
</tbody>
</table>

*Multivariable model adjusted for age, gender, race, education, BMI, ethanol and tobacco use, coronary heart disease, and physical activity. Model LR $\chi^2 = 407.7, P < 0.001.$*
Pathways

T2DM \(\rightarrow\) CKD \(\rightarrow\) ESRD
OBESITY

T2DM

HT

Lip

Metabolic Continuum

Prediabetes

IR

Inf

Continuum in Renal Disease?
Metabolic shock !!!!

Follow-up (months)

Hyperfiltering

Non Hyperfiltering
• Is all about BP and glucose control?
“Data were not fully explained by suboptimal metabolic or BP control since in the group with persistent hyperfiltration....

*blood glucose and HbA1c were* <125 mg/dL and <6.5% in 24% and 46.5% of patients

*and systolic and diastolic BP were* <130 and <80 mmHg in 24.3% and 38% of patients
Is albuminuria a marker of renal disease in T2DM?

- Al menos un 50% evoluciona a CKD en ausencia de albuminuria.
- No se puede predecir quién va a evolucionar a proteinuria o no.
3893 subjects; 920 (23.63%) with GFR < 60 ml/min.

- 55% normoalbuminuria
- 32% microalbuminuria
- 13% macroalbuminuria

Australia 2009

301 patients; 109 (36%) had < 60ml/min

39 % normoalbuminuria
35 % microalbuminuria
26 % macroalbuminuria
4421 patients; 529 (12%) had < 60ml/min
14 % normoalbuminuria
26 % microalbuminuria
60 % macroalbuminuria

3297 patients; 506 (15%) had < 60ml/min
52 % normoalbuminuria
21 % microalbuminuria
27 % macroalbuminuria

Atherosclerosis Risk in Community (ARIC)

- 1871 patients (with normoalbuminuria and no CKD)
- Follow-up: 11 years.
- Outcome: incidence of CKD (<60ml/min)

- 217 subject developed CKD
  - 125 (58%) normoalbuminuria.
  - 92 (42%) micro-macroalbuminuria.

Bash L. Et al Arch Intern Med. 2008
• 78 patients with <30ml/min/1.73m²

22 % normoalbuminuria;
88% microalbuminuria
macroalbuminuria
3893 subjects; 920 (23.63%) with < 60 ml/min.

- 55% normoalbuminuria
- 32% microalbuminuria
- 13% macroalbuminuria

30%-50% of the patients with ESRD have T2DM

No major changes during the last decades

Despite improvements in glucose and BP control and spread use of ACE inhibitors
Non-proteinuric GFR decline

3.37 vs 1 ml/min

accelerated GFR decline
Gender differences

- Sex is a major determinant of age-related GFR decline.

- Females are “protected” against this decline.

- Males vs Females: 8.7 vs 1.4 ml/min per decade.
Gender and GFR decline in non diabetics subjects

<table>
<thead>
<tr>
<th></th>
<th>MEN</th>
<th>WOMEN</th>
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<tbody>
<tr>
<td>Albuminuria</td>
<td>-0.581</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glucose</td>
<td>-0.096</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist</td>
<td>0.102</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>-0.064</td>
<td>0.003</td>
</tr>
<tr>
<td>Tot Chol /HDL</td>
<td>-0.129</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-----</td>
<td>-----</td>
</tr>
</tbody>
</table>

Halbesma N et al, PREVEND study, KI 2008
Animal models

- **Models of T1DM**: STZ-induced diabetes, 17β-estradiol attenuated diabetic glomerulosclerosis and tubulointerstitial fibrosis.

- **Models of T2DM**: (OZR) estrogen accelerated renal damage and increased triglycerides-induced renal injury in female animals.

- Estrogens may interact with insulin resistance traits i.e. dyslipidemia, in inducing renal damage in female patients?