Nephropathy in Type 1 Diabetes: Can One Identity the Patients at Risk?

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Cuba, November 2007
Nephropathy in Type 1 Diabetes

- It has been known for years that the risk of nephropathy is not the same for all patients with Type 1 diabetes
- Are they favouring or protective factors?
- Our Group has addressed this question in three studies that will be briefly reviewed.
Nephropathy in Type 1 Diabetes

• Factors predictive of nephropathy in DCCT Type 1 diabetic patients with good or poor metabolic control (Zhang et al: Diabet. Med. 2003, 20: 580-585)

• Different patterns of insulin resistance in relatives of Type 1 diabetic patients with retinopathy or nephropathy (Hadjaj et al: Diabetes Care, 2004, 27: 2661-2668)*


*Collaboration with the Group of M. Marre in Paris
Factors predictive of nephropathy in DCCT Type 1 patients

Zhang, Krzentowski, Albert and Lefèbvre, Diabetic Medicine 2003
The DCCT Study

• Design in the full-scale clinical trial:

- Total 1441 type 1 diabetic patients (13-39 years)
  - Primary prevention cohort: 726 patients
  - Secondary intervention cohort: 715 patients

Randomization:
- Intensive: CSII (continuous subcutaneous insulin infusion) or multiple daily injections of insulin
- Conventional: up to 2 daily injections of insulin

Intensive: n = 348, Conventional: n = 378
Intensive: n = 363, Conventional: n = 352

Intensive: CSII (continuous subcutaneous insulin infusion) or multiple daily injections of insulin
Conventional: up to 2 daily injections of insulin.
Metabolic Control and Complications

- Diabetes Control and Complications Trial (DCCT, 1983-1989)

Microalbuminuria (solid lines) and albuminuria (dotted lines)
Aims of the Work

- Questions:

  Some patients
  \[
  \text{Under GMC} \xrightarrow{\text{develop}} \text{Nephropathy}
  \]
  \[
  \text{Under PMC} \xhookleftarrow{\text{free from}} \text{Nephropathy}
  \]

- Aims:

  To assess the risk of a given patient developing diabetic nephropathy despite good metabolic control (GMC) or the chance of escaping nephropathy despite poor metabolic control (PMC)
A great example of Democracy in Science

DCCT Database made available by the US National Technical Information Service of the Dpt. of Commerce
The DCCT Study

- Risk covariates at baseline:
  - Quantitative variables
    - Age at entry (year)
    - BMI (kg/m²)
    - Duration of diabetes (months)
    - HbA₁c at baseline (%) 
    - AER (mg/24h)
    - Stimulated C-peptide (pmol/ml)
    - Mean blood glucose (mg/dl)
    - Arterial blood pressure (mmHg)
  - Categorical variables
    - Gender
    - Adulthood
    - Family history
    - Marital status
    - Smoking status
  - Time-related variables (HbA1c, AER, …….)
Definition of GMC or PMC

All DCCT patients irrespective of treatment

Good metabolic control
20% of DCCT patients

Poor metabolic control
20% of DCCT patients

HbA1c level: 6.9% 9.5%
Diabetic Nephropathy

- **Aims:** To assess the risk of developing nephropathy in patients maintained for several years under GMC or PMC.

- **Patients:** DCCT primary and secondary cohort under GMC or PMC but without nephropathy at baseline (n = 545).

- **Definition:** An observed urinary albumin excretion rate (AER) $\geq 40$ mg/24h *(measured annually)*.
Diabetic Nephropathy

• The database

Good metabolic control (GMC)  n = 277 in the study

12 (4.2%) excluded

Poor metabolic control (PMC)  n = 268 in the study

18 (6.3%) excluded

n = 289

n = 286

n = 545
Diabetic Nephropathy

- The effect of MC confirmed by Kaplan-Meier curve:

After 9 years: 15% developed nephropathy in GMC
52% did not develop nephropathy in PMC
Diabetic Nephropathy

- Factors predictive of nephropathy in backward stepwise Cox PH regression when adjusted for MC:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coef (± SE)</th>
<th>P</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single effects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>−0.094 (± 0.016)</td>
<td>&lt; 0.0001</td>
<td>0.91 (0.88-0.94)</td>
</tr>
<tr>
<td>AER (mg/24h)</td>
<td>0.54 (± 0.15)</td>
<td>0.0004</td>
<td>1.72 (1.27-2.31)</td>
</tr>
<tr>
<td>Duration of diabetes (months)</td>
<td>0.41 (± 0.12)</td>
<td>0.0011</td>
<td>1.50 (1.18-1.91)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>−0.10 (± 0.034)</td>
<td>0.0025</td>
<td>0.90 (0.84-0.96)</td>
</tr>
<tr>
<td>Gender (0 = male; 1 = female)</td>
<td>0.73 (± 0.35)</td>
<td>0.0389</td>
<td>2.07 (1.04-4.11)</td>
</tr>
<tr>
<td><strong>Interaction effects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age × MC</td>
<td>0.064 (± 0.013)</td>
<td>&lt; 0.0001</td>
<td>1.07 (1.04-1.09)</td>
</tr>
<tr>
<td>Gender × MC</td>
<td>−1.05 (± 0.40)</td>
<td>0.0091</td>
<td>0.35 (0.16-0.77)</td>
</tr>
</tbody>
</table>

The interaction terms: the major role of MC
the differential effects of age and gender.
Diabetic Nephropathy

- A risk ratio $\lambda = \exp(R)$:

$$R = 0.54 \times \log(AER) + 0.405 \times \log(\text{Disease duration}) - 0.103 \times \text{BMI} - 0.0943 \times \text{Age} + 0.0635 \times \text{Age} \times \text{MC} + 0.725 \times \text{Gender} - 1.05 \times \text{Gender} \times \text{MC}$$

GMC (MC = 0)

$$R = 0.54 \times \log(AER) + 0.405 \times \log(\text{Disease duration}) - 0.103 \times \text{BMI} - 0.0943 \times \text{Age} + 0.725 \times \text{Gender}$$

**Under GMC**

The risk of developing nephropathy is higher in women (risk ratio = 2.1) and decreases with age (risk ratio = 0.91).

1 = female; 0 = male *
Diabetic Nephropathy

- A risk ratio $\lambda = \exp(R)$:

$$R = 0.54 \times \log(AER) + 0.405 \times \log(\text{Disease duration}) - 0.103 \times \text{BMI} - 0.0943 \times \text{Age} + 0.0635 \times \text{Age} \times \text{MC} + 0.725 \times \text{Gender} - 1.05 \times \text{Gender} \times \text{MC}$$

PMC (MC = 1)

$$R = 0.54 \times \log(AER) + 0.405 \times \log(\text{disease duration}) - 0.103 \times \text{BMI} - 0.0308 \times \text{Age} - 0.325 \times \text{Gender}$$

* 1 = female; 0 = male. Risk ratio: 0.97 for age and 0.72 for gender

Under PMC

Male patients are more at risk of developing nephropathy than female patients.
Diabetic Nephropathy

- Example:
  Man 1, 35 years old, disease duration: 60 months
  BMI: 23 kg/m², AER: 15 mg/24h.

GMC (MC = 0)

\[ R = -2.55 \]
\[ \lambda = \exp(R) = 0.08 \]

PMC (MC = 1)

\[ R = -0.33 \]
\[ \lambda = 0.72 \]
Conclusions (1)

- In patients with good metabolic control (HbA1c ≤ 6.5% for 9 years), diabetic nephropathy occurred in 15% of the patients.
- Despite poor metabolic control (HbA1c ≥ 9.5% for 9 years), diabetic nephropathy did not develop in 52% of the patients.
Conclusions (2)

- Regardless of metabolic control, the risk of diabetic nephropathy is increased with:
  - Higher AER (within the «normal range») at baseline
  - Longer duration of diabetes
  - Lower BMI
Conclusions (3)

• Under good metabolic control, the risk of diabetic nephropathy seems higher in women than in men and decreases with age
• Under poor metabolic control, the effect of age vanishes and the risk of diabetic nephropathy seems higher in men ...
Take-home message 1

- It is confirmed that Type 1 diabetic patients with good MC may develop diabetic nephropathy and that those with poor MC may escape the condition.
- Higher AER, within the «normal range» already indicate early DR.
- Risk of DN is higher at younger age and lower BMI.
- The effect of gender is ambiguous.
Different patterns of insulin resistance in relatives of Type 1 diabetic patients with retinopathy or nephropathy

Hadjaj, Péan, Gallois, Passa, Aubert, Weekers, Rigalleau, Bauduceau, Bekherraz, Roussel, Dussol, Rodier, Maréchaud, Lefèbvre, and Marre for the GENESIS France-Belgium Study

Diabetes Care 2004
Genesis Franc-Belgium Family Study

- 853 subjects recruited
- 578 relatives
- 275 probands: -130 with
  -145 without diabetic nephropathy
Nephropathy stages

• Absent: repeated microalbuminuria < 30mg/24 h
• Incipient: microalbuminuria 30-300mg/24h
• Established: AER > 300mg/24h with creatinine <150µmol/l
• Advanced: increased AER, Creatinine > 150µmol/l or renal replacement
« Insulin resistance score » in first degree relatives

- Composite score taking into consideration:
  - History of hypertension
  - Dyslipidemia
  - Type 2 diabetes
  - Body weight

*Diabetes Care, 2004
Results

• Nephropathy in the probands correlated with:
  - Insulin resistance score in first degree relatives \((p<0.04)\), particularly in mothers \((p=0.02)\)
  - Personal history of Type 2 diabetes \((p<0.0001)\), obesity \((p<0.0001)\) and lipid disorders \((p<0.007)\), but not hypertension, in first degree relatives
Clustering of risk factors in parents of patients with nephropathy and Type 1 diabetes

- Earl et al, 1992: CVD
- De Cosmo et al, 1997: risk factors for CVD
- Tarnow et al, 2000: CVD
- Verhage et al, 1999: Syndrome X
- Lindsey et al, 1999: stroke
- Fagerudd et al, 1999: Type 2 DM
- Thorn et al, 2007: Hypertension, CVD and Type 2 DM
Take-home message 2

The risk of diabetic nephropathy in patients with Type 1 diabetes seems to be increased if one or both parents have experienced:

- Cardiovascular disease
- Type 2 diabetes
- Metabolic Syndrome/Insulin resistance
- Hypertension (?)
Diabetic nephropathy development is conditioned by the Glu298Asp polymorphism of endothelial nitric oxide synthase gene (NOS3): Additive effect with angiotensin-converting enzyme gene (ACE) I/D polymorphism

Weekers, Hadjaj, Guilloteau, Gallois, Pean, Roussel, Antkoche, Tichet, Lefèbvre and Marre on behalf of GENEDIAB and DESIR Study Groups, 2007: submitted
A candidate gene study among many others

- Endothelial nitric oxide synthase (eNOS) is a key regulator of renal hemodynamics. Is there an association with DN and two polymorphisms of the eNOS gene (NOS3)?
- Angiotensin-converting enzyme (ACE) insertion/deletion polymorphism is a risk factor for DN, the ACEII genotype conferring the lowest risk.
- Is there a combined effect of these 2 polymorphisms?
Angiotensin-I converting enzyme insertion/deletion polymorphism and its association with diabetic nephropathy: a meta-analysis of studies reported between 1994 and 2004 and comprising 14,727 subjects

Review of the results of 47 studies in 14,727 subjects
Risk of DN is 22% lower in subjects with II Genotype than Carriers of the D-allele.
The association is more marked (-35%) in diabetic Asians (Chinese, Japanese, Koreans)
Prospective study

- 297 Type 1 diabetic patients followed at the Angers (France) diabetes clinic for 7 years
- Primary outcome: diabetic nephropathy (see Study 2)
Results

• eNOS: exon 7 polymorphism (Asp/Asp patients versus Glu allele carriers) was associated with a lower risk of DN progression: HR 0.32, 95% CI 0.11-0.96
• ACE: II genotype was also associated with a lower risk of DN progression: HR 0.27, 95% CI 0.08-0.86
• The lowest risk was associated with the combination of ACE II and NOS3 Asp/Asp genotypes
OP 11 Nephropathy: mechanisms

0061

EURAGEDIC study: identification of new candidate genes for diabetic nephropathy


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New candidates: PARP1 (glucose-induced apoptosis)
SLC12A3 and EDN1 (renal Na excretion and systemic blood pressure)
Original Article

Genome-Wide Scans for Diabetic Nephropathy and Albuminuria in Multiethnic Populations

The Family Investigation of Nephropathy and Diabetes (FIND)


Diabetes, 2007, 56: 1577-1585
Take-home message 3

• Potential candidate genes underlying susceptibility to, or protection from, diabetic nephropathy have been indentified

• Large genome scan investigations are in progress to map genes involved in multiethnic populations
Diabetic Nephropathy

• Conclusions:
  – Under GMC, nephropathy develop in patients with specific baseline pattern. By contrast, patients with PMC can remain free from the complication for a long time period.
  – Major role of MC on time to nephropathy
  – Baseline risk factors: AER, age, gender, BMI and duration of diabetes. Diabetic nephropathy may already be present at AER < 40mg/24 hours
  - The effect of age: younger patients are associated with nephropathy.
  – The effect of gender: under GMC, women tend to develop nephropathy more often but appear to be better protected under PMC.