Albuminuria versus GFR as markers of diabetic CKD progression

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Evolution of Diabetic CKD

- **Normoalbuminuria** (AER < 20 µg/min)
- **Microalbuminuria** (AER 20-200 µg/min)
- **Macroalbuminuria** (AER > 200 µg/min)

GFR 100 (ml/min)

Log AER

Incipient Nephropathy

Overt Nephropathy

GFR 10 15 20 yrs

Normal
# Stages of CKD

<table>
<thead>
<tr>
<th>Stage</th>
<th>eGFR (ml/min/1.73 m²)</th>
<th>Description</th>
<th>Predominant AER status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&gt; 90</td>
<td>Kidney damage with normal/high GFR</td>
<td>Normo- Micro-</td>
</tr>
<tr>
<td>2</td>
<td>60-89</td>
<td>Kidney damage with mild reduction in GFR</td>
<td>Micro-</td>
</tr>
<tr>
<td>3</td>
<td>30-59</td>
<td>Kidney damage with moderate reduction in GFR</td>
<td>Micro/Macro-</td>
</tr>
<tr>
<td>4</td>
<td>15-29</td>
<td>Kidney damage with severe reduction in GFR</td>
<td>Macro-</td>
</tr>
<tr>
<td>5</td>
<td>&lt; 15</td>
<td>Kidney failure</td>
<td></td>
</tr>
</tbody>
</table>
Albuminuria versus GFR as markers of diabetic CKD progression

1. Albuminuria as a predictor of diabetic CKD
2. GFR as a predictor of diabetic CKD
3. Albuminuria & GFR uncoupling/coupling
4. Summary
Albuminuria as a marker of diabetic CKD progression

- High Variability
- Low Specificity
- Spontaneous Regression
- $\Delta \text{AER} \neq \Delta \text{GFR}$
Long-term Renal Outcomes of Patients With Type 1 Diabetes Mellitus and Microalbuminuria

An Analysis of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Cohort

Arch Intern Med. 2011;171(5):412-420
Higher levels of urinary albumin excretion within the normal range predict faster decline in glomerular filtration rate in diabetic patients

Babazono T et al. Diabetes Care 2009;32:1518-1520

![Graph showing adjusted rate of change in eGFR with geometric mean urinary albumin excretion categories.](image)
## Albuminuria versus GFR as markers of diabetic CKD progression

1. Albuminuria as a predictor of diabetic CKD
2. GFR as a predictor of diabetic CKD
3. Albuminuria & GFR uncoupling/coupling
4. Summary
GFR as index of diabetic CKD progression

- Low Variability
- High Specificity
- Infrequent Regression
- GFR = best index of kidney function
CKD-EPI formula underestimates measured GFR > 90 ml/min/1.73m$^2$ to the same extent as the MDRD formula in type 2 diabetes

RJ MacIsaac (unpublished)
Possible regression of eGFR with bardoxolone

Pergola PE NEJM 2011, 28, 327-36
Albuminuria versus GFR as markers of diabetic CKD progression

1. Albuminuria as a predictor of diabetic CKD
2. GFR as a predictor of diabetic CKD
3. Albuminuria & GFR uncoupling/coupling
4. Summary
AER vs isotopic GFR in Type 2 Diabetes

RJ MacIsaac et al Diabetes Care 2004

Normoalbuminuria: n=192, 39%
Microalbuminuria: n=109, 35%
Macroalbuminuria: n=109, 26%
AER vs eGFR in Type 1 Diabetes
ME Molitch et al Diabetes Care, 33, 1536-1543 2010
Microalbuminuria and the risk for early progressive renal function decline in type 1 diabetes
Perkins BA et al. JASN 2007, 18, 1353-1361

Baseline GFR (ml/min/1.73m²)

<table>
<thead>
<tr>
<th></th>
<th>155</th>
<th>143</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normoalbuminuria</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>○</td>
<td>△</td>
</tr>
</tbody>
</table>

Early decline GFR > - 3.3%/year

○ Stable
○ Early decline
△ ESRD

GFR > - 3.3%/year

9% 31%
Early Renal Function Decline in Type 2 Diabetes

Pavkov ME et al CJASN 2011

% with early decline GFR > 3.3%/year (urinary iothalamate clearance)

Initial GFR > 150 ml/min

32%  
Normoalbuminuria (n = 68)

42%  
Microalbuminuria (n = 88)
Microalbuminuria and the risk for early progressive renal function decline in type 1 diabetes

Perkins BA et al. JASN 2007, 18, 1353-1361

Frequency of early progressive renal function decline in patients with T1DM and normoalbuminuria or microalbuminuria divided according to the 4-year course of microalbuminuria

![Bar graph showing frequency of early progressive renal function decline](image)
Early Renal Function Decline in Type 2 Diabetes

Pavkov ME et al CJASN 2011

Decline in early renal function and subsequent development of ESRD is strongly dependent on progression to macroalbuminuria in type 2 diabetes

<table>
<thead>
<tr>
<th></th>
<th>Normoalbuminurina (ACR &lt;30 mg/g)</th>
<th>Microalbuminurina (ACR 30 to &lt;300mg/g)</th>
<th>Macroalbuminurina (ACR ≥300 mg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RFD−, %</td>
<td>8.4 (2 events)</td>
<td>6.1 (2 event)</td>
<td>39.5 (6 events)</td>
</tr>
<tr>
<td>RFD+, %</td>
<td>0</td>
<td>11.9 (2 events)</td>
<td>74.8 (31 events)</td>
</tr>
</tbody>
</table>

Forty-three of 49 cases of ESRD occurred during this period. The cumulative incidence is presented according to albuminuria levels at the end of the initial period. The initial period was used to determine the presence or absence of renal function decline. In the follow-up period these participants were followed for ESRD according to the previously defined GFR slope. RFD−, no renal function decline; RFD+, renal function decline; ACR, urinary albumin/creatinine ratio.
Relationship between initial change in AER and overall change in GFR per year in type 1 diabetes: Intention to treat analysis


23 study groups (9 studies)
Early DN
n=1181

10 study groups (5 studies)
Late DN
n=510

a  r = -0.10, p = 0.33

b  r = -0.67, p = 0.034
**Intensified multifactorial intervention in patients with T2 DM and microalbuminuria: STENO 2 Study**


### Analysis according to intention to treat (n=160)

<table>
<thead>
<tr>
<th></th>
<th>Standard n = 80</th>
<th>Intensive n = 80</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median AER (mg/24h)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>69</td>
<td>78</td>
</tr>
<tr>
<td>3.8 yr</td>
<td>79</td>
<td>66*</td>
</tr>
<tr>
<td>7.8 yr</td>
<td>99</td>
<td>58* (p &lt; 0.01)</td>
</tr>
<tr>
<td><strong>Mean iGFR (ml/min/1.73m²)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>118</td>
<td>116</td>
</tr>
<tr>
<td>3.8 yr</td>
<td>105</td>
<td>105</td>
</tr>
<tr>
<td>7.8 yr</td>
<td>86</td>
<td>86</td>
</tr>
</tbody>
</table>
Intensified multifactorial intervention in patients with T2 DM and microalbuminuria: STENO 2 Study


<table>
<thead>
<tr>
<th>Post Hoc Analysis: according to AER during follow-up (n = 151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline AER</td>
</tr>
<tr>
<td>Follow-up AER</td>
</tr>
<tr>
<td>n = 46</td>
</tr>
<tr>
<td>GFR Decline (ml/min/year)</td>
</tr>
</tbody>
</table>

**Conclusion** Remission to normoalbuminuria is associated with decreased GFR decline during 7.8 yr follow-up
Albuminuria and GFR as markers of diabetic CKD progression

1. Albuminuria as predictor of diabetic CKD
2. Estimating or measuring GFR in diabetic CKD
3. Albuminuria & GFR uncoupling/coupling
4. Summary
Conclusions

• Both albuminuria and GFR should be assessed as markers of diabetic CKD progression

• Changes in albuminuria are variable whereas changes in GFR are usually progressive

• A decline in GFR is usually accompanied by a rise in albuminuria but some patients follow a non-albuminuric pathway to renal impairment (GFR < 60 ml/min/1.73m$^2$)

• Progression to ESRD is usually strongly dependent on progression to macroalbuminuria

• Albuminuria and GFR have complementary roles in staging and stratifying the risk of progressive diabetic CKD
The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report


| Composite ranking for relative risks by GFR and albuminuria (KDIGO 2009) | Albuminuria stages, description and range (mg/g) |
|---|---|---|
| GFR stages, description and range (ml/min per 1.73 m²) | A1 | A2 | A3 |
| G1 | High and optimal | >105 | | |
| | 90–104 | | |
| | 75–89 | | |
| G2 | Mild | 60–74 | | |
| G3a | Mild-moderate | 45–59 | | |
| G3b | Moderate-severe | 30–44 | | |
| G4 | Severe | 15–29 | | |
| G5 | Kidney failure | <15 | | |
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