مرکز تحقیقات نفرولوژی قطب علمی آموزشی نفرولوژی

In The Name of God

Microalbuminuria & Kidney Outcome

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Center of Excellence in Nephrology

KDIGO

Kidney Int Suppl. 2013;3:19.

Chapter 1: Definition & classification of CKD

The **NL AER**: <30 mg/day (20 mcg/min)

Persistent AER: 30 - 300 mg/day (20 to 200 mcg/min) **moderately increased albuminuria** (microalbuminuria) that persists in **2 or 3** test over a **3 to 6-month** period.

AER: >300 mg/day (200 mcg/min) **severely increased albuminuria** (macroalbuminuria).

Tests?

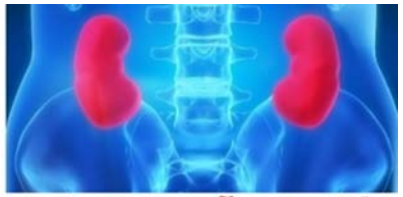
1-Urinary protein excretion from a 24 h collection

2-Urinary alb excretion from a 24 h collection

3-Urinary alb excretion from a first morning timely void

4-Alb/Cr ratio from a first morning void

4^{th} test has the strongest association with the risk for renal events.



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Why Microalbuminuria is Important?

1982
Viberti, G. C.

AER of 87 patients with IDDM was measured in 1966-67.

14 years later clinical information & cause of death were recorded.

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They saw that development of overt proteinuria was related to the 1966-67 AER values (2 of 55 patients with AER<30 μg/min VS 7 of 8 with AER 30 - 140 μg/min).

24 times higher…

9·1% of AER <30 μg/min had died, VS 37·5% with higher AER.

Conclusion:

Elevated levels of microalbuminuria strongly predict the development of clinical diabetic nephropathy & death.

1982 Viberti, G. C. MICROALBUMINURIA AS A PREDICTOR OF CLINICAL NEPHROPATHY IN INSULIN-DEPENDENT DIABETES MELLITUS

1984 (N Engl J Med 1984; 310:356–60.)
Mogensen, C. E.
Microalbuminuria Predicts Clinical Proteinuria and Early Mortality in Maturity-Onset Diabetes

In 1973, four group of patients were evaluated:

-NL controls (AER <15 μg/ml),

-Diabetic patients with AER: 16 to 29 μg alb/ml

-76 patients with morning urine specimens with AER: 30 to 140 μg/ml &

-Diabetic patients with AER: >140 μg/ml alb/ml.

After 9 years the group of

30 to 140 μg/ml was **more** likely to have **clinically detectable proteinuria (>400 μg/ml)** than were the groups with lower concentrations &

Mortality was **148% of** NL controls.

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They conclude that microalbuminuria in NIDDM is predictive of clinical proteinuria & increased mortality.

1984 (N Engl J Med 1984; 310:356–60.)

Mogensen, C. E.

Microalbuminuria Predicts Clinical Proteinuria and Early Mortality in Maturity-Onset Diabetes

1988

Yudkin, JohnS

MICROALBUMINURIA AS PREDICTOR OF VASCULAR DISEASE IN NON-DIABETIC SUBJECTS: Islington Diabetes Survey

Q:

The relation between MICROALBUMINURIA and vascular disease

Patients:

187 subjects aged over 40 selected from 1084 cases attending a diabetic screening project.

Results:

1- Microalbuminuria in 23% of diabetics VS 9·4% of nondiabetics.

2-Weak relation between microalbuminuria & BP & in F/U…

3-Coronary heart disease 74% VS 32·9% (OR: 6·38, 95% CI: 1·91-21·4).

4-Peripheral vascular disease 44% VS 9·7% (OR: 7·72, 95% CI: 2·14-27·8).

5-Deaths: 33% VS 2·0% (OR: 24·33, 95% CI: 5·40-109·7) among microalbuminurics.

1988 Yudkin, JohnS MICROALBUMINURIA AS PREDICTOR OF VASCULAR DISEASE IN NON-DIABETIC SUBJECTS: Islington Diabetes Survey

1992 Messent, Jeannie W. C. Prognostic significance of microalbuminuria in IDDM: A 23 year follow-up study

A 23 year cohort/63 IDDM & AER in 1967.

1981: Clinical proteinuria in microalbuminurics developed 87% VS 4%.

1990: Risk of clinical proteinuria in microalbuminurics become higher (RR= 9.3, 95% CI: 1.36 to 10.3, P < 0.05)

Dying from a cardiovascular cause was higher (RR: 2.94, 95% CI: 1.18 to 7.34, P <0.05).

Risk of renal failure was higher but *not* significant(RR: 3.31, 95% CI: 0.72 to 15.24, NS).

1992
Messent, Jeannie W. C.

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Table 1. Clinical characteristics of the 63 insulin-dependent diabetic patients first assessed for albumin excretion rate in 1967

Baseline characteristics	Initial AER in 1967	
	AER < 30 μg/min	AER ≥ 30 ≤ 140 μg/min
No. of subjects (M, F)	55 (36, 19)	8 (5, 3)
AER *μg/min*	4.77 (0.4–21.8)	68.5 (39.0–140)
Age *years*	39.2 ± 1.7	41.4 ± 1.7
Duration of diabetes *years*	8.8 ± 1.0	14.1 ± 2.9

Patients are divided into 2 groups with microalbuminuria (initial AER ≥ 30 ≤ 140 μg/min) and normoalbuminuria (initial AER < 30 μg/min).

1992
Messent, Jeannie W. C.

Table 2. Clinical outcome of 61 of the 63 insulin-dependent diabetic patients after 23 year follow-up

	Initial AER in 1967	
	AER < 30 μg/min	AER ≥ 30 ≤ 140 μg/min
Proteinuria	5/53 (9.4%)	7/8 (87.5%)
Renal failure	4/53 (7.5%)	2/8 (25%)
Total mortality	17/53 (32%)	5/8 (62.5%)
Non-cardiovascular deaths	8/53 (15.1%)	1/8 (12.5%)
Cardiovascular deaths	9/53 (17%)	4/8 (50%)
Age at death *years*	66.6 ± 2.8	58.2 ± 2.5
Duration of diabetes at death *years*	33.2 ± 4.2	29.9 ± 1.2

1994

Post-exercise Albuminuria Does Not Predict Microalbuminuria in IDDM

Bognetti, E.

Can post-exercise UAE in IDDM predict the development of microalbuminuria?

NO! *does not* predict the onset of microalbuminuria

1994

Neugebauer, S.Baba, T.Watanabe, T.Ishizaki, T.Kurokawa, K.

Evaluation of N-acetyltransferase NAT2 gene polymorphism as a marker for microalbuminuria in NIDDM?

The genotype distribution was studied in Japanese NIDDM patients with

1-Established nephropathy (n = 43),

2-Microalbuminuria (n = 24),

3-Normoalbuminuria (n = 18),

4-Non-diabetic patients with kidney disease (n = 62), &

5-Healthy control subjects (n = 51).

Neugebauer, S.Baba, T.Watanabe, T.Ishizaki, T.Kurokawa, K.

The prevalence of the genotype, encoding the slow acetylator phenotype (M1, M2, M3), was

7.0% in Group1,

20.8% in Group2,

0% in Group3,

6.5% in Group4 &

7.8% in Group5.

The differences were non-significant & NAT gene polymorphism can not be a risk marker for diabetic nephropathy in Japanese NIDDM patients.

1997 Mogensen, CarlErik Prevention of Diabetic Renal Disease with Special Reference to Microalbuminuria
A Chapter of a book (The Kidney and Hypertension in DM)
pp 539-549

-500,000 ESRD are registered & DM is the leading cause of them.

-Prevention has emerged as a key issue &

-Focused on early detection by evaluation of microalbuminuria has recommended.

1998 Initial UAE determines the progression of microalbuminuria in patients with type-2 diabetes and normotensive BP values despite improved metabolic control

Eibl, N.

This study has investigated the **effect of BS control** on the **progression diabetic nephropathy** in relation to **initial UAER levels**.

Patients with NIDDM divided into two groups:

Group 1 (n=10 UAER: 51±35 mg/24 h) &

Group 2 (n=10 UAER: 191±175 mg/24 h).

Despite a significant BS control by insulin (HbA1c: group1: 11±1.5 vs. 7.9±1.2%; group 2: 10.6±0.9 vs. 9.1±1.3%, P<0.001),

Progression of UAER

Was observed in group 2 (191±175 vs. 331±237 mg/24 h, P<0.02),

But not in group 1 (51±35 vs. 41±24 mg/24 h).

1998
Eibl, N.

Result

In normotensive NIDDM *the initial UAE levels determine* it's *progression.*

1998 another study

Incidence and Determinants of Microalbuminuria in Koreans With Type 2 Diabetes
Park, Joong-Yeol

Evaluation of microalbuminuria in 188 Korean with initial normoalbuminuric NIDDMs.

F/U: 5.5 ± 0.9 years.

146 patients finished study,

37 showed persistently elevated UAE (>20 μg/min) during follow-up (52/1,000 person-years).

1998 Park, Joong-Yeol

CONCLUSIONS

Age, duration of DM, HbA1C, retinopathy & BP are risk factors for development of microalbuminuria in Korean NIDDM .

1999

Intensified multifactorial intervention in patients with type 2 DM & microalbuminuria: the Steno type 2 randomised study

Gæde, Peter

They carried out a randomised trial of stepwise

-Standard treatment (Danish guidelines) **(n=80) or**

-Intensive treatment (behaviour modification, pharmacological therapy targeting hyper-glycaemia, HTN, dyslipidaemia & microalbuminuria) **(n=80)**

of risk factors in patients with microalbuminuria.

Patients in intensive group had significantly lower rates of progression to

- **-Nephropathy** (OR 0·27 [95% CI 0·10–0·75]),
- **-Retinopathy** (0·45 [0·21–0·95]), **and**
- **-Autonomic neuropathy** (0·32 [0·12–0·78]) **than those in the standard group.**

1999

Gæde, Peter

1999

The CCB Nitrendipine Attenuates Renal & Glomerular Hypertrophy in Diabetic Rats

Nielsen, B.

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Female Wistar rats were randomised into 4 groups:

1- Diabetic on Placebo &

2- Non-diabetic on Placebo

3- Diabetic on Nitrendipine (250 mg/kg)

4- Non-diabetic on Nitrendipine (250 mg/kg)

for 8 weeks.

1999
Nielsen, B.

Conclusion

Administration of **nitrendipine** to diabetic rats for 8 weeks had a **inhibitory effect** on **renal and glomerular hypertrophy** & showed a tendency towards a **reduction in UAE** ($p = 0.06$) ***without*** affecting BS control or **systemic BP**.

2002

Microalbuminuria Reduction With Valsartan in Patients With Type 2 Diabetes Mellitus: A Blood Pressure–Independent Effect

Viberti, Giancarlo

332 patients with NIDDM & microalbuminuria, with or without HTN, were randomly assigned to 80 mg/d valsartan or 5 mg/d amlodipine for 24 weeks.

2002Viberti, Giancarlo

One of Results

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The UAER at 24 weeks was 56% (95% CI, 49.6 to 63.0) of baseline with valsartan and 92% (95% CI, 81.7 to 103.7) of baseline with amlodipine, a highly significant between-group effect (P<0.001).

Valsartan lowered UAER similarly in both the hypertensive and normotensive subgroups.

2004

Reduced GFR in asymptomatic diabetic patients Predictor of increased risk for cardiac events independent of albuminuria

Knobler, Hilla

In 269 asymptomatic patients, baseline evaluation included diabetes-related complications, **including CrCl & albuminuria**.

During follow-up (2.3 years), all cardiac events were recorded.

35% of the reduced GFR group had normoalbuminuria.

2004

Knobler, Hilla

Patients with reduced GFR had a significant increase in cardiac events (unstable angina, nonfatal MI & cardiac procedures) (25% vs. 13%, p = 0.019)

Multivariate analysis found that reduced GFR was an independent predictor of cardiac events (OR 2.2, 95% CI 1.1 to 4.46).

2006

Risk Factors for Renal Dysfunction in Type 2 Diabetes: U.K. Prospective Diabetes Study 74

Retnakaran, Ravi

UKPDS

5,102 NIDDM

4,031 Without albuminuria

5,032 With NL PCr.

After 15 years

1,544 (38%) of 4,031 patients developed albuminuria and 1,449 (29%) of 5,032 developed renal impairment.

Of 4,006 patients with the requisite data for both outcomes, 1,534 (38%) developed albuminuria and 1,132 (28%) developed renal impairment.

Of the latter, 575 (51%) did not have preceding albuminuria.

2006

Retnakaran, Ravi

Additional independent risk factors for albuminuria were increased baseline systolic BP, PCr, Indian-Asian ethnicity, male sex, increased waist circumference, TG, LDL Ch, HbA1C, increased WBC count, ever having smoked & previous retinopathy.

2011

The relationship between mean platelet volume with microalbuminuria and glycemic control in patients with type II diabetes mellitus

Ünübol, Mustafa. Journal Platelets

Microalbuminuria is the predictor of diabetic nephropathy & microangiopathy [with mean platelet volume (MPV)] in NIDDM.

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Subjects underwent laboratory analyses and their MPV, HbA1c, serum Cr, FBS & postprandial BS & 24-h urine alb were recorded.

The study included 354 patients with NIDDM.

2011
Ünübol, Mustafa
Journal Platelets

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They determined positive correlation between MPV and 24-hour urine microalbuminuria ($r=0.14$, $p=0.009$).

2013

Does Microalbuminuria has Positive Predictive Value in Patients With Essential Hypertension for Renovascular Hypertension?

Zülfükar YILMAZ

Microalbuminuria as an indicator for renovascular HTN?

330 hypertensive patients were divided into 2 groups:

-Microalbuminuria &

-Normoalbuminuria & examined by doppler US & then MR angiography.

Results:

Microalbuminuria was detected in 107 of 330 (32.42%).

Mean CrCl (108,14±19,83 vs 116,36±18,62, p=0,002) were significantly lower in microalbuminurics.

3/107 (2.80%) of the patients had RAS in the group of patients with microalbuminuria and 8/223 (3.58%) of the patients had RAS in the group of patients with normoalbuminuria.

2013

Zülfükar YILMAZ

Conclusion:

Microalbuminuria isn't an indicator for renovascular HTN.

2014

Microalbuminuria: target for renoprotective therapy PRO
Roscioni, Sara S.

Data supporting the use of microalbuminuria as a valid surrogate end point (Instead of ESRD & decreased GfR & …) in trials of CKD &

This point that albumin is a toxic molecule for tubular cells in the kidney.

2015

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

Porrini, Esteban

Accepting microalbuminuria as a surrogate marker for renal outcomes will:

- **Lead to less resource-consuming trials,**
- **Accelerate the development & access of drugs for CKD.**

2015
Porrini, Esteban

-They have shown that

GFR can start to decline before albuminuria.

-Risk factors might contribute to GFR deterioration are:

-Female sex,

-Obesity,

-Dyslipidaemia (in particular hyperTG),

-HTN &

-Glomerular hyperfiltration &…

In NIDDM

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Prevalence of Microalbuminuria in NIDDM approximately 10 years after the diagnosis ranges from 25 to 40%.

In NIDDM

In ADVANCE trial (11,140 Pts) was 27% &

In another systematic review of 28 studies (10,298 Pts) was 26% at a mean diabetes duration of 10 years.

There are racial and ethnic differences in the rate of macroalbuminuria.

According to UKPDS

In 5100 Pts with new NIDDM,

6.5% had Microalbuminuria &

0.7% had Macroalbuminuria.

Annual rate of progression from NL to Microalbuminuria was 2%.

A higher rate of Microalbuminuria (17.9%) was noted in another report.

In UKPDS

-Rate of Microalbuminuria was significantly higher in hypertesives (24% versus 14%).

-Rate of Microalbuminuria was in olders.

-At 10 years

-Macroalbuminuria was 5.3% &

-Microalbuminuria was 25%.

-Rate of progression from micro to macroalbuminuria was 2.8%/year.

Regression to Normal

As with IDDN, in NIDDM microalbuminuria can regress to NL albuminuria.

Factors associated with remission:

-Short duration of microalbuminuria

-Better BS control

-Better BP control

-Use of ACEis or ARBs

-Lower Ch & TG

-Levels of albuminuria

-Less glomerular hyperfiltration.

In NIDDM

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Yearly measurement of urine alb/Cr ratio is recommend.

In IDDM

The development of **microalbuminuria** usually begins **5 to 15 years** after the onset of DM.

A small proportion of patients develop **microalbuminuria** within < 5 years of disease onset.

In IDDM

In a systematic review of 7938 IDDM, prevalence of microalbuminuria was 28% at a mean duration of 15 years.

In another report, the prevalence of microalbuminuria reached 52% at 30 years.

Risk factors of microalbuminuria in IDDM:

- -Higher AER, even in NL range
- -Worse BS control
- -Higher systolic or mean arterial pressure
- -Presence & severity of retinopathy
- -Total or LDL-ch
- -History of smoking

Some patients with normoalbuminuria or microalbuminuria have significant reductions in GFR prior to the development of macroalbuminuria.

In IDDM

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Microalbuminuria increases the risk of

- **Macroalbuminuria ,**
- **Retinopathy,**
- **Neuropathy and**
- **Increases overall mortality.**

Summary

-NL AER: <30 mg/day

-Microalbuminuria: 30 - 300 mg/day

-Macroalbuminuria: >300 mg/day

-Alb/Cr ratiois best test & has the strongest association with the risk for renal events.

-Different study show microalbuminuria predict macroalbuminuria, CHD, PVD, lower GFR & higher Mortality.

-Early detection & treatment of microalbuminuria is recommended.

-Regression of microalbuminuria to NL is possible & Short duration of microalbuminuria, BS & BP control, ACEis or ARBs, Lower Ch & TG, Levels of albuminuria & Less glomerular hyperfiltration help to this regression.