
بسم الله الرحمن الرحیم

# Approach to Microalbuminuria in Diabetic Nephropathy

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# Introduction and definition

Microalbuminuria is the first detectable clinical sign of kidney involvement in diabetic patients.it involves between 20-40% of diabetic people after 10-15 years of diabetes mellitus onset. Since the microalbuminuria appears, it will progress to proteinuria in 20-50% of patients in about 10-15 years.

In patients with microalbuminuria ,reductin in kidney function is variable.but mean reduction in GFR is 10-12cc/min/year .kiney involvement process is stage to stage and microalbuminuria is potentially reversible .

the urine dipstick is an insensitive marker for initial protein excretion, not becoming positive until protein excretion exceeds 300 to 500 mg/day. Using a specific assay for albumin is a more sensitive technique. The normal rate of albumin excretion is less than 30 mg/day(20mcg/min).

persistent albumin excretion between 30 and 300 mg/day (20 to 200mcg/min) or albumin to creatinin ratio between 2.5-35 mg/mmol in men and 3-35 mg/mmol in women is called microalbuminuria . In diabetic patients, ,microalbuminuria is a risk marker for cardiovascular mortality and morbidity. It may be some times,not always,an early marker of diabetic nephropathy.

# Diagnosis and Detection of Microalbuminuria

Establishing the diagnosis of microalbuminuria requires the demonstration of an elevation in albumin excretion that persists over a three- to six-month period. In this period, microalbuminuria should be possitive in 2or more than 2 tests.Fever,execise ,heart failure, and poor glycemic control are among the factors that can cause transient increases in albuminuria.

Although the 24-hour urine collection was the initial gold standard for the detection of microalbuminuria, it has been suggested that screening can be more simply achieved by a timed urine collection or measurement of the urine albumin concentration on an early morning Specimen to minimize changes in urine volume that occur during the day.

Microalbuminuria is unlikely if the albumin excretion rate is below 20 mcg/min in a timed collection or the urine albumin concentration is less than 20 to 30 mg/L in a random specimen. Higher values (particularly those just above this range) may represent false positive results, and should be confirmed by repeated measurements.

**There are also a variety of semiquantitative dipsticks, such as Clinitek Microalbumin Dipsticks and Micral-Test II test strips, which can be used to test for microalbuminuria if urine albumin excretion cannot be directly measured. The reported sensitivity and specificity of these tests range from 80 to 97 percent and 33to 80 percent,respectively.**

**One problem with measuring the urine albumin concentration or estimating it with a sensitive dipstick is that false negative and and false positive results can occur, since the urine albumin concentration is determined by the urine volume and the amount of albuminuria .**

**The confounding effect of the urine volume can be minimized by repeated measurements on early morning specimens.**

**Measurement of the urine albumin-to-creatinine ratio in an untimed urinary sample is the preferred screening strategy for microalbuminuria in all diabetic patients.**

**This test has the following advantages: it gives a quantitative result that correlates with the 24-hour urine values over a wide rannge of protein excretion, it is simple to perform and inexpensive, and repeat values can be easily obtained to ascertain that microalbuminuria, if present,is persistent.**

**Limitations of urine albumin to creatinin ratio:**

**-The optimal time to measure the urine albumin-to-creatinine ratio is uncertain.g iven the uncertainty, we have a slight preference for first morning void specimens. If this is inconvenient, specimens can be obtained at other times during the day. There are no data about the timing of repeat measurements as the patient's course is being monitored. If possible, it seems preferable to obtain the samples at approximately the same time of day.**

-Vigorous exercise can cause a transient increase in albumin excretion As a result, patients should refrain from vigorous exercise in the 24 hours prior to the test.

-The accuracy of the urine albumin-to-creatinine ratio will be diminished if creatinine excretion is substantially different from the expected value; this is particularly important in patients with borderline values.

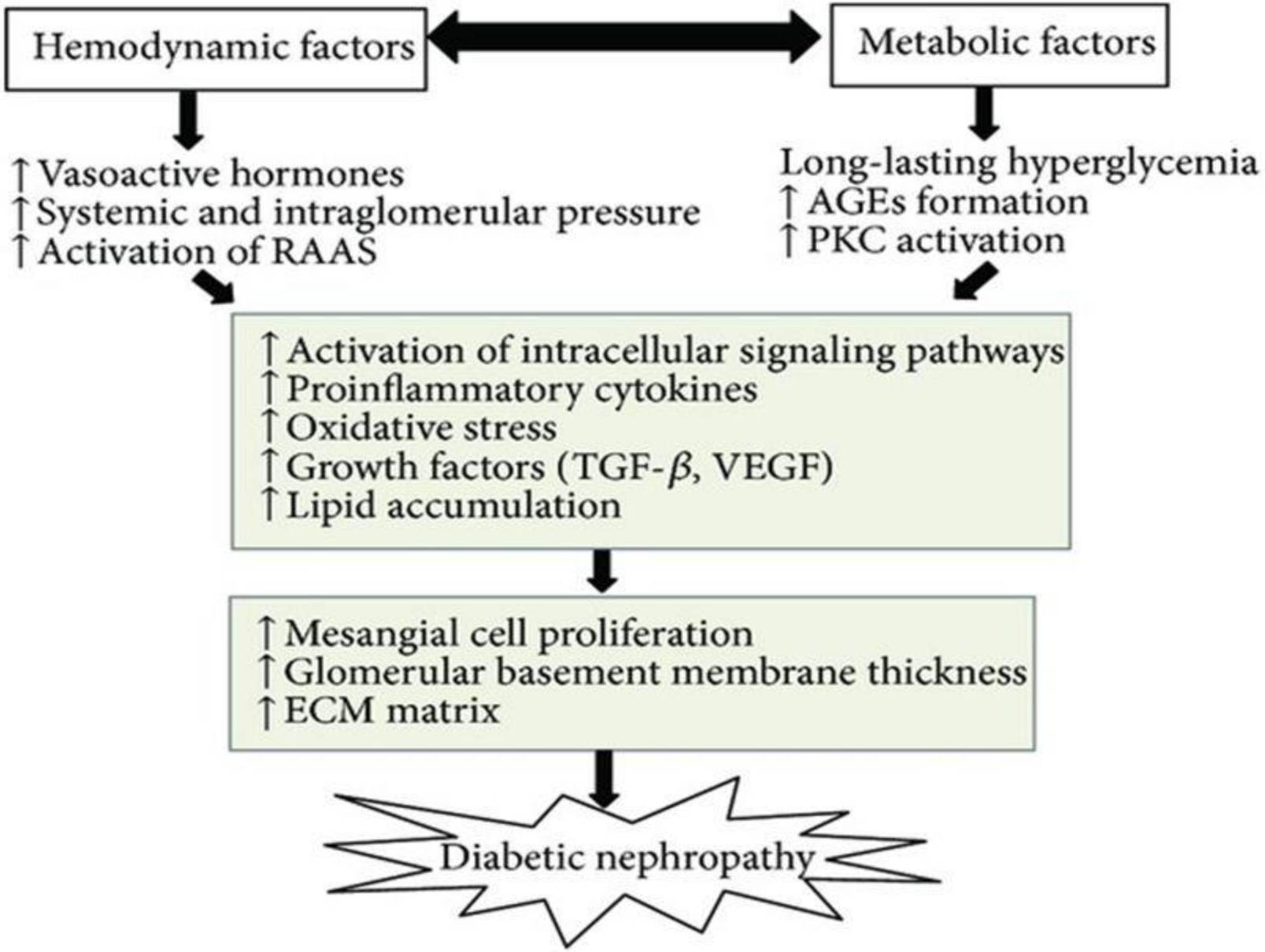
Albumin excretion will be underestimated in a muscular man with a high rate of creatinin excretion and overestimated in a cachectic patient in whom muscle mass and creatinine excretion are markedly reduced.

The ratio also varies with race/ethnicity in the United States, as creatinine excretion is significantly higher among non-Hispanic blacks and mexican Americans than among non-Hispanic whites.

## Mechanisms

Diabetes can induce abnormalities in all the three distinct layers of the glomerular membrane-endothelial cell layer, basement membrane and podocyte layer. These abnormalities can be structural e.g. increased pore size or biochemical e.g. loss of negatively charged molecules. Recently, the importance of the glycocalyx for macromolecular transvascular transport has been documented. The glycocalyx is a thick layer of proteoglycan/glycosaminoglycan that cover the outer endo-thelial layer in the kidney and in the other capillary beds of the body.

**Poor glycaemic regulation and diabetes reduce the glycocalyx, leading to micro- and macroalbuminuria. Studies in diabetic animals and man have demonstrated raised measured and estimated capillary hydraulic pressure. Tubular proteinuria is characterized by massive increase in urinary excretion of small proteins e.g. b2-microglobulin, while albumin excretion is only slightly increased. Urinary b2- microglobulin excretion is either normal or only slightly elevated in diabetes.**


Hemodynamic factors
Metabolic factors
↑ Vasoactive hormones
↑ Systemic and intraglomerular pressure
↑ Activation of RAAS
Long-lasting hyperglycemia
↑ AGEs formation
↑ PKC activation
↑ Activation of intracellular signaling pathways
↑ Proinflammatory cytokines
↑ Oxidative stress
↑ Growth factors (TGF-β, VEGF)
↑ Lipid accumulation
↑ Mesangial cell proliferation
↑ Glomerular basement membrane thickness
↑ ECM matrix
Diabetic nephropathy

# RELATIONSHIP OF PROINFLAMMATORY CYTOKINES WITH MICROALBUMINURIA IN PATIENTS OF TYPE 2 DIABETES MELLITUS- IMPLICATIONS IN THE PATHOGENESIS OF DIABETIC NEPHROPATHY

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## ABSTRACT

### BACKGROUND

Type 2 diabetes mellitus is frequently associated with an increased inflammatory state. However, the relationship between of low grade inflammation and diabetic nephropathy still remains unclear with conflicting results. We therefore intended to analyse the inter-relationships between pro inflammatory cytokines and renal functions with respect to the glycemic status in type 2 diabetes mellitus patients.

### MATERIALS AND METHODS

89 type 2 Diabetes mellitus patients and 26 age matched healthy controls were studied (29 normoalbuminuric, 33 microalbuminuric and 27 proteinuric) and their levels of proinflammatory cytokines (IL-6 and TNF α) were measured and correlated with albuminuria and glycosylated haemoglobin.

### RESULTS

Urinary albumin excretion showed positive correlation with the levels of Interleukin-6 ($r=0.711$ $P<0.001$), as well as Tumour Necrosis Factor Alpha ($r=0.591$; $P < 0.005$) in the diabetics. The glycosylated haemoglobin had a positive correlation with Il-6 ($r=0.792$, $P<0.001$) and Urinary albumin excretion rate ($r=0.685$, $P < 0.001$) and mild positive correlation with TNF-α ($r= 0.589$, $P<0.005$). There was no such correlation observed among control subjects.

### CONCLUSION

The study shows that pro inflammatory cytokines levels are elevated in early diabetic nephropathy and are independently associated with urinary albumin excretion thus it can be hypothesized that their local release play a role in the renal damage in the development of renal damage.

## Natural history of microalbuminuria in diabetes mellitus

Recent studies have suggested that the original prognostic significance assigned to the finding of microalbuminuria no longer applies to the majority of patients with DKD.

In the early 1980s, the finding of microalbuminuria was reported to be associated with a risk of progression to overt proteinuria (macroalbuminuria) of 60–80% over 6 to 14 years in people with type 1 diabetes.3 More contemporary studies have shown microalbuminuria **remission rates of 21–64% in people with type1 or type2 diabetes** . For example ,in a recent analysis of the Diabetes Control and Complications Trial /Epidemiology of Diabetes Interventions and Complications (DCCT/EDIT) study,325 participants with type1 diabetes developed incident persistent microalbuminuria.

The 10 year cumulative incidences of progression to macroalbuminuria and regression to normoalbuminuria were %28 and %40 ,respectively.

The **modern history of microalbuminuria is more frequently of remission/regression** rather than progression to overt proteinuria.

In addition, in patients with type 1 or type 2 diabetes and microalbuminuria with preserved renal function ,there is **no correlation between microalbuminuria and the patterns of injury that can be seen in renal tissue obtained by biopsy**.

Independent risk factors for regression of microalbuminuria include better glycemic control,lower blood pressure, lower serum cholesterol and triglyceride levels,recent onset of microalbuminuria,a lessr degree of albuminuria,lower baseline glomerular filtration rate (GFR; ie, less glomerular hyperfiltration), and, on renal biopsy,smaller increase in glomerular basement membrane width and treatment with an ACEI.

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# Regression and progression of microalbuminuria in adolescents with childhood onset diabetes mellitus

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Purpose: Although microalbuminuria is considered as an early marker of nephropathy in diabetic adults, available information in diabetic adolescents is limited. The aim of this study was to investigate prevalence and frequency of regression of microalbuminuria in type 1 (T1DM) and type 2 diabetes mellitus (T2DM) patients with childhood onset.

Methods: One hundred and nine adolescents (median, 18.9 years; interquartile range (IQR), 16.5–21.0 years) with T1DM and 18 T2DM adolescents (median, 17.9 years; IQR, 16.8–18.4 years) with repeated measurements of microalbuminuria (first morning urine microalbumin/creatinine ratios) were included. The median duration of diabetes was 10.1 (7.8–14.0) years and 5.0 (3.5–5.6) years, respectively, and follow-up period ranged 0.5–7.0 years. Growth parameters, estimated glomerular filtration rate, glycosylated hemoglobin (HbA1c) and lipid profiles were obtained after reviewing medical record in each subject.

Results: The prevalence of microalbuminuria at baseline and evaluation were 21.1% and 17.4% in T1DM, and 44.4% and 38.9% in T2DM. Regression of microalbuminuria was observed in 13 T1DM patients (56.5%) and 3 T2DM patients (37.5%), and progression rate was 10.5% and 20% in T1DM and T2DM respectively. In regression T1DM group, HbA1c at baseline and follow-up was lower, and C-peptide at baseline was higher compared to persistent or progression groups. In T2DM, higher triglyceride was observed in persistent group.

Conclusion: Considerable regression of microalbuminuria more than progression in diabetes adolescents indicates elevated urinary microalbumin excretion in a single test does not imply irreversible diabetic nephropathy. Careful monitoring and adequate intervention should be emphasized in adolescents with microalbuminuria to prevent rapid progression toward diabetic nephropathy.

Keywords: Albuminuria, Type 1 diabetes mellitus, Type 2 diabetes mellitus, Child, Adolescent

## Screening for microalbuminuria in diabetes

screening for microalbuminuria in type 1 and type 2 diabetes is **worthwhile in order to prevent progression to renal failure.** This conclusion relies on the fact that **anti-hypertensive therapy in microalbuminuric patients may attenuate progression, even in normotensive individuals.** Cost benefit analyses for microalbuminuria screening in type 1 diabetes suggests that assuming a treatment benefit of 10%, screening would be economically neutral, and any benefit over this **would lead to increased life expectancy and reduced ESRF**. In type 2 diabetes, the argumente for screening for microalbuminuria is less strong,but nevertheless widely acknowledged as beneficial and recommended by many international guidelines.

Screening for microalbuminuria has the fundamental problem that intra-individual variability of AER is very wide, and varies according to diet, exercise and temperature. Timed urine collections are too cumbersome for routine clinical care, so spot samples (preferably first morning void samples) are used and in order to allow for urine concentration, the albumin content is corrected for creatinine giving an albumin:creatinine ratio (ACR). A positive ACR on two or more occasions is enough to confirm the diagnosis of diabetic renal disease (ACR >2.5 in males and >3.5 in females). This is suggested as giving a sensitivity of 96% and a specificity of 99.7% for the presence of diabetic nephropathy.

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# Comparison of Urine Albumin-to-Creatinine Ratio (ACR) Between ACR Strip Test and Quantitative Test in Prediabetes and Diabetes

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**Background:** Albuminuria is generally known as a sensitive marker of renal and cardiovascular dysfunction. It can be used to help predict the occurrence of nephropathy and cardiovascular disorders in diabetes. Individuals with prediabetes have a tendency to develop macrovascular and microvascular pathology, resulting in an increased risk of retinopathy, cardiovascular diseases, and chronic renal diseases. We evaluated the clinical value of a strip test for measuring the urinary albumin-to-creatinine ratio (ACR) in prediabetes and diabetes.

**Methods:** Spot urine samples were obtained from 226 prediabetic and 275 diabetic subjects during regular health checkups. Urinary ACR was measured by using strip and laboratory quantitative tests.

**Results:** The positive rates of albuminuria measured by using the ACR strip test were 15.5% (microalbuminuria, 14.6%; macroalbuminuria, 0.9%) and 30.5% (microalbuminuria, 25.1%; macroalbuminuria, 5.5%) in prediabetes and diabetes, respectively. In the prediabetic population, the sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy of the ACR strip method were 92.0%, 94.0%, 65.7%, 99.0%, and 93.8%, respectively; the corresponding values in the diabetic population were 80.0%, 91.6%, 81.0%, 91.1%, and 88.0%, respectively. The median [interquartile range] ACR values in the strip tests for measurement ranges of <30, 30-300, and >300 mg/g were 9.4 [6.3-15.4], 46.9 [26.5-87.7], and 368.8 [296.2-575.2] mg/g, respectively, using the laboratory method.

**Conclusions:** The ACR strip test showed high sensitivity, specificity, and negative predictive value, suggesting that the test can be used to screen for albuminuria in cases of prediabetes and diabetes.

**Key Words:** Albuminuria, Albumin-to-creatinine ratio, Prediabetes, Diabetes, Strip test

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## when begin screening for microalbuminuria in diabetes

**In type1 diabetes:5 years after diagnosis and then annualy**

**In type2 diabetes:at diagnosis ,then annualy**

**For screening we should measure Alb/Cr ratio in a spot urine sample.**

**The American Diabetes Association and National Kidney Foundation recommend annual sceening for**

**Microalbuminuria in children from 9 years of age with 5 years of insulin dependent diabetes mellitus (IDDM)**

**duration, from 11 years of age with 2 years of IDDM duration, and adolescent with 2 years or more of IDDM**

**duration.**

# Screening for Microalbuminuria in Patients with Diabetes

## Why?

- To identify patients with diabetic kidney disease (DKD).
- To distinguish DKD patients from diabetic patients with chronic kidney disease (CKD) *from other causes*. The latter require further investigation and possibly different clinical management.
- Because *markers of kidney damage* are required to detect early stages of CKD. Estimated glomerular filtration rate (eGFR) alone can only detect CKD stage 3 or worse.

## When?

Begin screening:

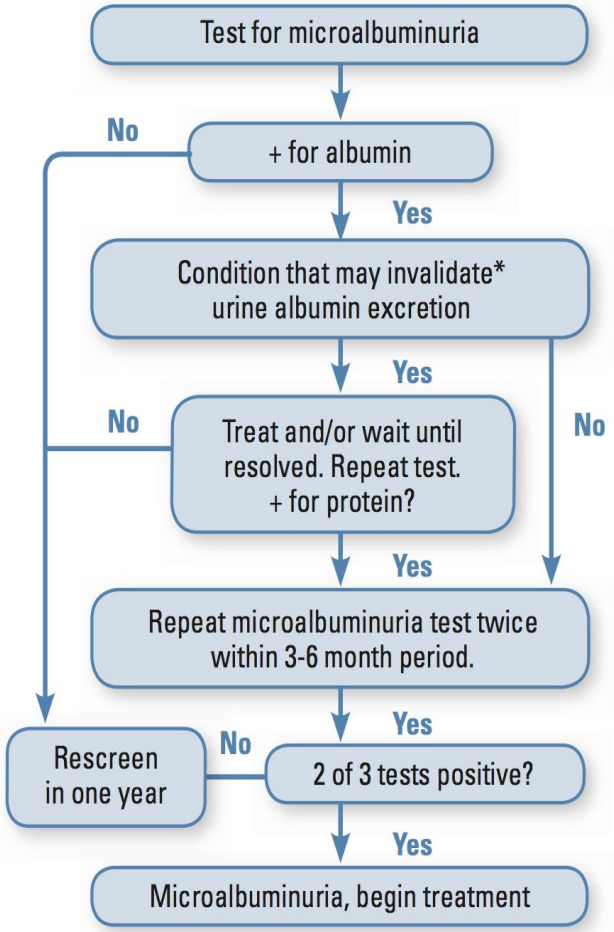
- In type 1 diabetes – 5 years after diagnosis, then annually
- In type 2 diabetes – at diagnosis, then annually

## Is it Microalbuminuria?

**Measure urinary albumin-creatinine ratio (ACR) in a spot urine sample.**

| Category | Spot (mg/g creatinine) |
|---|---|
| Normoalbuminuria | <30 |
| Microalbuminuria | 30-300 |
| Macroalbuminuria | >300 |

## How?




* Exercise within 24 hours, infection, fever, congestive heart failure, marked hyperglycemia, pregnancy, marked hypertension, urinary tract infection, and hematuria.

**prevention**

**Glycemic control**

Strict glycemic control is recommended in all patients with **type 1 diabetes** because of its beneficial effects **on microvascular complications.**

**worse glycemic control is a risk factor for both the development of microalbuminuria and for progression to macroalbuminuria in type 2 diabetic patients.**

Several randomized trials have demonstrated **that strict glycemic control is effective for the primary prevention of microalbuminuria.**

The **UKPDS** evaluated the importance of strict glycemic cxontrol in 3867 patients with newly diagnosed type 2 diabetes. The patients were randomly assigned to intensive or conventional therapy.

**intensive insulin therapy was associated at 9 years f/u with a significantiy lower rate of microalbuminuria and macroalbuminuria.**

Benefit from intensive therapy was also noted in the **ADVANCE** trial in which 11,140 patients with type2 diabetes were randomly assigned to intensive therapy to achieve a hemoglobin A1c below %6.5 or to standard therapy.

At a median follow-up of five years, the intensive and standard groups achived mean hemoglobin A1c values of 6.5 and 7.3 percent, respectively. **Intensive therapy was associated with a small but significant reduction in the rate of new-onset microalbuminuria.**

**The efficacy of ACEI & ARBS in prevention of microalbuminuria in type1 diabetic patients**

**Four randomized, placebo-controlled trials** of 256 to 3326

Patients With **type 1 diabetes and normoalbuminuria**

(Adolescent Type1 Diabetes Cardio-Renal Intervention Trial

[**AdDIT**], Renin Angitensin System Study[**RASS**],

Examining Use of Ticagrelor in Peripheral Artery Disease

[**EUCLID**],and Diabetic Retinopathy Candesartan Trials

[**DIRECT**], **showed no benefit from angiotensin inhibition**.

**there is no evidence that ACE inhibitors or ARBs are effective for the primary prevention of microalbuminuria in patients with type 1 diabetes who are normoalbuminuric and normotensive.**

These patients should be screened yearly for microalbuminuria after five years and **angiotensin inhibition initiated if persistent microalbuminuria is documented.**

## The efficacy of ACEI & ARBS in prevention of microalbuminuria in type2 diabetes

There have been variable results related to the efficacy of ACE inhibitors or ARBs for the primary prevention of microalbuminuria in clinical trials of patients with type2 diabetes.

The following findings have been noted in different trials of patients

With type2 diabetes with normal albumin excretion at baseline.

The data are presented according to whether the baseline blood pressure is normal or elevated.

### Normotensive patients

In the normotensive Appropriate Blood pressure Control in Diabetes (ABCD) trial of 480 patients, the rate of progression to microalbuminuria was significantly lower with enalapril compared With placebo and with nisoldipine compared with placebo, but after five years, there was no significant difference.

The rate of progression to microalbuminuria was equivalent with enalapril and nisoldipin.

In DIRECT Protect-2,which included 725 normotensive patients with normal albuminuria, the rate of progression to Microalbuminuria was nonsignificantly lower with candesartan compared with placebo(29 versus 40% at 4.7 years).

**These observations do not permit a conclusion about the efficacy of angiotensin inhibition for the prevention of new onset microalbuminuria in normotensive patients with type2 diabetes.**

**We suggest not treating with an ACEI or ARB solely for the prevention of microalbuminuria in such patients.**

**These patients should be screened yearly for microalbuminuria and an ACEI or ARB initiated if persistent microalbuminuria is documented.**

The 2012 KDOQI guidelines for diabetes and CKD36 and the 2014 ADA guidelines do **not recommend using ACE inhibitors or ARBs for the primary prevention of diabetic kidney disease in normotensive patients with normoalbuminuria.**

# Hypertensive patients

-In the **BENEDICT** trial, 1204 type2 diabetes patients with a mean baseline blood pressure of 150/87 mmHg were randomly assigned to **trandolapril**,**verapamil**,the **combination** of these medications,or **placebo**.

The rate of **new onset** microalbuminuria at three years or more was significantly lower with trandolapril alone or with verapamil(6 and 5.7 percent, respectively) than with verapamil alone or placebo (11.9 and 10.0 percent respectively).

-In the **ADVANCE** trial of 11,140 type2 diabetes patients, a fixed combination regimen of **perindopril-indapamide** significantly reduced the rate of new-onset microalbuminuria(19.6 vs 23.6%).

These patients had a mean baseline blood pressure of 145/81 mmHg, and perindopril-indapamide therapy was assigned with a significantly grater mean reduction in blood pressure (5.6/2.2mmHg) compared with placebo.

In the aggregate, these trials suggest that **ACE inhibitors and ARBs are effective in preventing the new onset of microalbuminuria in hypertensive patients with type 2 diabetes** and the **BENEDICT trial provides support for these drugs being more effective than at least verapamil**

## Treatment of microalbuminuria in diabetes mellitus -Multi factorial intervention

numerous studies have demonstrated a renoprotective effect of improved **glycaemic regulation, arterial blood pressure reduction, blockade of the reninangiotensin system independent of blood pressure and intensified multifactorial intervention—with tight glucose control and the use of renin-angiotensin system blockers, aspirin and lipid-lowering agents.**

The benefit of screening for microalbuminuria and the implementation of multifactorial intervention targeting lifestyle factors (**smoking, diet, and exercise) as well as hyperglycaemia, lipids and blood pressure including blockade of RAS**) ,was demonstrated in the **Steno 2 study** of **microalbuminuric type 2 diabetes** patients.**intensive therapy reduced both microvascular and macrovascular disease.**

With respect to diabetic nephropathy, **there were significant improvements in albumin excretion** (-20 versus +30mg/day) and **progression to macroalbuminuria** (20 versus 39 percents).

# Treatment of microalbuminuria

## Glycemic control

**Strict control of the serum glucose** concentration (**A1C less than 7.5 percent**)

can slow the rate of progression or even reduce proteinuria in these patients,

compared to a common increase in protein excretion in conventionally treated patients.

In the **DCCT**, intensive glycemic control reduced the onset of

microalbuminuria and macroalbuminuria by 34% and 56% .In the intensive versus conventional blood glucose control,the **risk of progression of nephropathy is decreased by 80% both in type 1 &2 DM.**

## Reduction in protein intake

Strong evidence indicates that high dietary protein intake increases risk of diabeticNephropathy & its progression to ESRD. Lower intake of proteins has a lower incidence of albuminuria. It reduces Hyperfiltration & intraglomerular pressure.**ADA** recommends 0.8 gr/kg in **diabetic nephropathy**.

***Lipid lowering therapy***

There is experimental evidence to suggest that **hypercholesterolaemia** may play a pathogenic role in **progressive glomerular injury.** There is also evidence to suggest that reduction in cholesterol can reduce the rate of decline of GFR in patients with diabetic nephropathy. Reduction of AER in normotensive ,microalbuminuric type 2 diabetic patients has also observed on **statin** therapy, and improved oxidative stress has also been noted.

**Smoking cessation**

in both type I & II -It affects **renal Hemodynamics**, Increases **Catecholamines** production. Patients With DM I & II who smoke have a greater risk of **Ualb, and progression to ESRD is about twice** as rapid than non-smokers.

# Smoking and MA

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Metabolism

www.metabolismjournal.com


## Smoking cessation predicts amelioration of microalbuminuria in newly diagnosed type 2 diabetes mellitus: a 1-year prospective study

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ABSTRACT

The objective of the study was to assess the effect of smoking cessation on microalbuminuria in subjects with newly diagnosed type 2 diabetes mellitus (DM). From 500 smokers newly diagnosed with type 2 DM and microalbuminuria, only 193 (96 men/97 women; age, 56.4 ± 7.8 years) agreed to participate and were educated on smoking cessation, diet, and exercise. Pharmacological interventions were not different among the studied groups. All subjects were contacted by phone monthly with emphasis on smoking cessation. Anthropometric, biochemical parameters and urine specimens were obtained at baseline and at 12-month follow-up. *Microalbuminuria* was defined as an albumin to creatinine ratio of 30 to 299.9 μg/mg creatinine. Ankle brachial pressure index was determined by ultrasound. A total of 120 (62.2%) subjects quit smoking. Prevalence of microalbuminuria was reduced at 1 year to 72.6% in the subjects who quit smoking and to 22.5% in those who continued smoking ($P = .015$). Multivariate logistic regression analysis demonstrated that independently associated with the reduction in albumin to creatinine ratio (84.8 vs 28.7 μg/mg creatinine) were amelioration of glycemic control ($P < .001$), blood pressure ($P = .02$), dyslipidemia ($P = .02$), and insulin resistance ($P = .05$). Smoking cessation also reduced the prevalence of peripheral vascular disease ($P = .03$) and neuropathy ($P = .04$). From the pharmacological and lifestyle interventions, smoking cessation had the highest and an independent contribution to the reduction of microalbuminuria ($P < .001$). Smoking cessation in newly diagnosed type 2 DM patients is associated with amelioration of metabolic parameters, blood pressure, and the reduction of microalbuminuria. Stricter counseling about the importance of quitting smoking upon type 2 DM diagnosis is necessary to protect against the development of diabetic nephropathy and vascular complications.

## Angiotensin inhibition in type1 diabetes

Given the **appreciable rate of regression of microalbuminuria**, an **ACE inhibitor ARB can be given if there is evidence of progressively increasing albuminuria or the patient becomes hypertensive.**

The superiority of **ACE inhibitor** therapy in preventing renal events in patients with microalbuminuria is **unperoven**.

In a systematic review of 11 trials of normotensive type1 diabetic patients with microalbuminuria, ACE inhibitor therapy significantly reduced the risk of **progression to macroalbuminuria** and significantly increased the risk of **regression to normoalbuminuria**.

Data are lacking on the efficacy of ARBs in patients with type 1 diabetes and microalbuminuria.

It seems likely that these drugs are as effective as ACE inhibitors given their proven benefit in patients with type2 diabetes and either microalbuminuria or overt nephropathy.

An ARB can be substituted if the patient develop a persistent cough on an ACE inhibitor.

In a metaanalysis of 12 studies in diabetic normotensive patients with albuminuria,Long acting non Dihydropyridine CCB were as effective as ACEI in delaying the occurrence of macroalbuminuria in normotensive type1 diabetes mellitus who had persistent albuminuria.

## Other antihypertensive drugs in microalbuminuric type1 diabetes

Whether other antihypertensive drugs are as effective as ACE inhibitors or ARBs in preventing progressive

proteinuria in patients with type 1 diabetes and microalbuminuria is unproven. This issue was addressed

in a trial that randomly assigned 42 normotensive patients with type 1 diabetes and microalbuminuria(mean 64 mcg/min at baseline) to perindopril, slow-release nifedipine, or placebo.

At three years, median albumin excretion had fallen to 23 mcg/min in the perindopril group compared with

the rising values of 122 and 112 mcg/min in the other two groups.

Studies in patients with overt proteinuria have found that **only diltiazem and verapamil** may have as prominent

antiproteinuric activity as ACE inhibitors in diabetic patients.

# ACE inhibitors and ARBs in microalbuminuric type2 diabetic patients

**Renoprotective** benefits with ACE inhibitors and ARBs compared with placebo have been noted ina number of trials.

The potential magnitude of benefit can be illustrated by the results of a trial in wchich 590 hypertensive patients with type2 diabetesand microalbuminuria that were randomly assigned to eather **irbesartan** or **placebo** and then followed for two years.

The primary end point was the time from baseline to first detection of overt nephropathy (urine albumin excretion>200mcg/min) and **at least a 30% increase** from baseline on 2 consecutive visits.

This end point was significantly more common in the placebo group compared with irbesartan.

**ACE inhibitors and ARBs** have **similar efficacy** in type2 diabetic patients with microalbuminuria .

The only randomized comparative trial(**DETAIL**) of these agents in type 2 diabetic patients compared **enalapril** with the ARB **telmisartan** in 25o patients with early nephropathy as defined by albuminuria (82% microalbuminuria and 18% macroalbuminuria to a maximum 1.4 g/d) and abaseline GFR of approximately 93ml/min per1.73m2.

A greater fall in GFR of at least 10.0 mL/min per 1.73 m2 at5 years was predefined as suggesting a clinically significant difference between the two treatment groups.

At five years, there was a smaller decline in GFR with enalapril that was not significant .Both groups had **similar** rates or findings for the secondary end points, wchich included annual changes in the GFR,blood pressure,serum creatinin concentration,urinary albumin excretion and rates of end stage kidney diseases cardiovascular events and mortality.

## Calcium channel blockers

Calcium channel blockers have **less antiproteinuric** effect than ACE inhibitors or ARBs, and the antiproteinuric effect is **primarily** seen with **diltiazem and verapamil** (which are useful to reduce proteinuria in hypertensive patients),not the dihydropyridines. The difference between these drug classes in patients with type 2 diabetes and microalbuminuria was evaluated in the MARVAL trial in which 332 such patients were randomly assigned to valsartan or amlodipin.

Albumin excretion was reduced by 44 percent with valsartan compared to 8% with amlodipin, adifference that was highly significant. There was no difference in blood pressure between the two groups during the course of the study.

## Mineralocorticoid receptor antagonists

Blockade of the effect of aldosterone with mineralocorticoid receptor antagonists has been demonstrated to lower albuminuria in short term studies of patients with micro or macroalbuminuria, in addition to standard of care with angiotensin converting enzyme inhibitors or angiotensin II receptor blockers .

Recently, a new aldosterone blocking agent **finerenone** has been claimed to have the **same antiproteinuric effect as aldosterone blockers, but with a smaller risk for hyperkalemia.** In type 2 diabetic patients, a short term study demonstrated a dose dependent antiproteinuric effect up to 38% on top of standard of care, with less than 3% stopping because of potassium problems .

# Aldactone and Microalbuminuria

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## Article: Treatment

# Spironolactone diminishes urinary albumin excretion in patients with type 1 diabetes and microalbuminuria: a randomized placebo-controlled crossover study

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## Abstract

**Aims** Adding aldosterone receptor blockade to standard renoprotective treatment may provide additional renoprotection in patients with overt nephropathy. We expected an impact of spironolactone in early diabetic nephropathy, and for this hypothesis we studied the effect on markers of glomerular and tubular damage in patients with Type 1 diabetes and persistent microalbuminuria.

**Methods** A double-blind, randomized, placebo-controlled crossover study in 21 patients with Type 1 diabetes and microalbuminuria using spironolactone 25 mg or placebo once daily, for 60 days added to standard antihypertensive treatment. After each treatment period, the primary endpoint were evaluated: urinary(u)-albumin excretion/24 hour(h) and secondary endpoints; 24 h blood pressure, glomerular filtration rate (GFR) and markers of tubular damage: urinary liver-type fatty-acid binding protein (LFABP), neutrophil gelatinase associated lipocalin (NGAL) and kidney injury molecule 1 (KIM1).

**Results** All patients completed the study. During spironolactone treatment, urinary albumin excretion rate was reduced by 60% (range 21–80%), from 90 mg/24 h to 35 mg/24 h ($P = 0.01$). Blood pressure (24 h) did not change during spironolactone treatment ($P > 0.2$ for all comparisons). The GFR (SD) decreased from 78 (6) mL/min/1.73 $m^2$ to 72 (6) mL/min/1.73 $m^2$ ($P = 0.003$). Urinary liver-type fatty-acid binding protein, neutrophil gelatinase-associated lipocalin and kidney injury molecule 1 did not change during treatment ($P > 0.3$ for all comparisons). Treatment was well-tolerated, but two patients had severe hyperkalaemia (plasma potassium = 5.7 mmol/l), which was sufficiently treated with diuretics and dietary intervention.

**Conclusions** Spironolactone treatment in addition to standard renoprotective treatment lowers urinary albumin excretion in microalbuminuric patients with Type 1 diabetes, and thus may offer additional renoprotection independent of blood pressure.

## Glucagon-like peptide 1 receptor agonists

Glucagon-like peptide 1 receptor agonists are among the new glucose lowering agents with pleiotropic effects with a **potential benefit on the kidney**.

Short-term studies demonstrated reduction in albuminuria up to up to **30 %** with the glucagon-like peptide1 receptor agonist **liraglutide**.

In addition to the glucose lowering effect, beneficial effects on **blood pressure, body weight, inflammation and perhaps reduction in intraglomerular pressure,** have been suggested as explanatory factors.

The long-term cardiovascular outcome study with liraglutide **LEADER** (n = 9340) demonstrated a **22% reduction in the renal combined endpoints**. This result was driven primarily by the **new onset of persistent macroalbuminuria, which occurred in fewer participants in the liraglutide group.**

Another similar, but smaller (n = 3297) cardiovascular outcome study with the glucagon-like peptide 1 receptor agonist **semaglutide, SUSTAIN** also demonstrated reduction in **new or worsening nephropathy** to **3.8%** in the semaglutide group from 6.1% in the placebo group.

## Sodium glucose transporter 2 inhibitors

Sodium glucose transporter 2 inhibitors have also been suggested to have **favorable renal effects** in addition to lowering of glucose. As glucagon-like peptide 1 receptor agonists, they **lower blood pressure, albuminuria and body weight.** In contrast to the other effects, the glucose lowering effect decline with reduced renal function probably due to the need for a certain level of glomerular filtration rate to maintain the effect on blood glucose. **hyperfiltration** was ameliorated with **empagliflozin** in type 1 diabetes and may be very important for the potential renoprotective effect of this class of agents .

In the cardiovascular outcome trial with the sodium glucose transporter 2 inhibitor empagliflozin **EMPA-REG**, **incident or worsening nephropathy** occurred in 525 of 4124 patients (**12.7%**) in the empagliflozin group and in 388 of 2061 (**18.8%**) in the **placebo** group .In addition **to reduction in progression of albuminuria, a doubling of the serum creatinine level** occurred in **1.5%** of patients in the **empagliflozin** group and in **2.6%** of patients in the **placebo** group.

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ARTICLE

# The effect of sodium glucose cotransporter 2 inhibition with empagliflozin on microalbuminuria and macroalbuminuria in patients with type 2 diabetes

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**Abstract**

*Aims/hypothesis* Sodium glucose cotransporter 2 (SGLT2) inhibition lowers $HbA_{1c}$, systolic BP (SBP) and weight in patients with type 2 diabetes and reduces renal hyperfiltration associated with type 1 diabetes, suggesting decreased intraglomerular hypertension. As lowering $HbA_{1c}$, SBP, weight and intraglomerular pressure is associated with antialbuminuric effects in diabetes, we hypothesised that SGLT2 inhibition would reduce the urine albumin-to-creatinine ratio (UACR) to a clinically meaningful extent.

*Methods* We examined the effect of the SGLT2 inhibitor empagliflozin on UACR by pooling data from patients with type 2 diabetes and prevalent microalbuminuria (UACR = 30–300 mg/g; $n = 636$) or macroalbuminuria (UACR > 300 mg/g; $n = 215$) who participated in one of five phase III randomised clinical trials. Primary assessment was defined as percentage change in geometric mean UACR from baseline to week 24.

*Results* After controlling for clinical confounders including baseline log-transformed UACR, $HbA_{1c}$, SBP and estimated GFR (according to the Modification of Diet in Renal Disease [MDRD] formula), treatment with empagliflozin significantly reduced UACR in patients with microalbuminuria (−32% vs placebo; $p < 0.001$) or macroalbuminuria (−41% vs placebo; $p < 0.001$). Intriguingly, in regression models, most of the UACR-lowering effect with empagliflozin was not explained by SGLT2 inhibition-related improvements in $HbA_{1c}$, SBP or

## Endothelin receptor A antagonists

Blockade of the endothelin receptor A has been demonstrated to have **significant antiproteinuric** effects on top of renin–angion-tensin system blockade .The first endothelin receptor A blocker tested in a phase 3 study was **avosentan**. The study was stopped early because of problems with side effects related to fluid overload .

More recently, **atrasentan** was demonstrated in a short term study **RADAR** to lower **proteinuria** by an average of **38%** and reduced **albuminuria** at least **30%** in 55% of participants **without a difference in edema and heart failure** despite an increase in body weight.

Endothelin 1 antogonist **Atrasentan** Provides **Health Benefits** to Patients with Diabetic Nephropathy .**Low-dose atrasentan (0.75 mg/day) decreased albuminuria by 36% without major side effects** in a randomized trial of 211 type 2 diabetic nephropathy patients who received a placebo, low-dose atrasentan, or 1.25 mg/day atrasentan for 12 weeks.