ADS Position Statements

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Microalbuminuria in Diabetes

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SYNOPSIS
CORE FACTS IN CLINICAL DIABETIC NEPHROPATHY

1. Incipient diabetic nephropathy is defined as persistent levels of albumin excretion rate in the range 20-200μg/min (established microalbuminuria).

2. Clinically overt diabetic nephropathy occurs when albumin excretion rate persistently exceeds 200μg/min and when total proteinuria exceeds 0.5 grams/24 hours. This is approximately equivalent to a positive (1+) albustix test.

3. Screening for microalbuminuria may be performed on spot urine specimens using bedside test procedures (e.g. Micral Test).

4. Established microalbuminuria is generally defined as 2 out of 3 albumin excretion rate measurements in the range 20-200μg/min. This definition yields a sensitivity of approximately 90% and a specificity of 90% with a positive predictive value that is highly dependent on the prevalence of microalbuminuria in the study population. The positive predictive value decreases from 90% with 50% prevalence to 50% with 20% prevalence and to 18% with 2% prevalence of microalbuminuria.

5. If allowance is made for duration of disease, the incidence of diabetic nephropathy is similar in patients with type I and type II diabetes. This is based on studies in Pima Indians and in Germans although others have suggested a lower incidence of diabetic nephropathy in patients with type II diabetes.

6. Approximately 1/3 of patients with type I diabetes develop clinically overt diabetic nephropathy after an interval of 15-20 years following diagnosis. In these patients albumin excretion rate increases at an annual rate of 30-40%. Slower rates of progression are observed with longer duration of disease.

7. In the last 30 years there has been a decrease in the incidence of renal failure in type I diabetic patients but this has been balanced by an increasing incidence of renal failure in patients with type II diabetes.

8. In patients with microalbuminuria, the glomerular filtration rate may be increased or normal but it generally does not fall below the normal range before the onset of established diabetic nephropathy.

9. Microalbuminuria and macroalbuminuria are associated with vascular disease in both type I and type II diabetic patients. The risk for vascular death is increased over 30-fold in macroalbuminuric patients with type I diabetes.

10. A characteristic of patients with microalbuminuria is a small rise in blood pressure. In patients with type I diabetes, a rise in blood pressure often represents underlying nephropathy. In contrast, in type II diabetes, hypertension often precedes microalbuminuria

11. In type I diabetic patients with, intensified glycaemic control may lessen the rate of progression from microalbuminuria to established diabetic nephropathy. By contrast, intensified glycaemic control has not been proven to affect the progress of established diabetic nephropathy.

12. In type I diabetic patients with microalbuminuria, antihypertensive therapy reduces albumin excretion rates.

13. Effective antihypertensive therapy of type I diabetic patients with established nephropathy (to a mean blood pressure of 100mmHg) causes an approximate halving of the rate of fall of glomerular filtration rate and in albumin excretion rate.

14. Aggressive antihypertensive therapy of established diabetic nephropathy in patients with type II diabetes has shown a reduction in albumin excretion rate but no longterm data on preservation of renal function are available.

15. In general, most antihypertensive regimens have shown beneficial effects in patients with hypertension and incipient or established diabetic nephropathy. It is not yet clear if some classes of antihypertensive agents confer a specific benefit on the evolution of microangiopathy, in addition to their effect on systemic blood pressure.

16. Some antihypertensive agents, especially ACE inhibitors, have been shown to reduce microalbuminuria or delay progression to clinically overt nephropathy in normotensive patients.

PRACTICE RECOMMENDATIONS

1. Blood pressure should be measured in the supine position after 5 minutes rest at every visit in all diabetic patients.

2. Testing for microalbuminuria should be performed at least yearly in all diabetic patients.

3. The finding of a single Albumin Excretion Rate (AER) value in the rate 20-200µg/min as an indication for two additional measurements of AER in the next 6 weeks.

4. 2 out of 3 AER measurements in the range 20-200µg/min suggest the presence of incipient diabetic nephropathy in adult patients with type I diabetes >5 years after diagnosis.

5. The diagnosis of incipient nephropathy indicates that specialised referral should be considered, because of the high risk of vascular complications in these patients.

6. The possibility of non-diabetic renal disease as a cause of albuminuria and /or deteriorating renal function should be considered in patients without evidence of diabetic retinopathy, in the first 5 years after diagnosis of type I diabetes and in the presence of an active urine sediment or systemic illness. Renal biopsy needs to be considered in such patients.

7. In type I patients with micro or macroalbuminuria, antihypertensive therapy should be more aggressive than in non-albuminuria patients and treatment should be considered if supine blood pressure exceeds 140/90. The evidence for treatment of near normal blood pressure in microalbuminuric type II diabetes is less persuasive.

8. Protein restriction could be considered as a therapeutic option once serum creatinine levels are clearly elevated.

9. In microalbuminuric patients attention should continue to be directed at optimising glycaemic control, since near-normoglycaemia may retard the evolution of nephropathy.

10. Microalbuminuria may reflect widespread vascular disease. Therefore, attention should be given to the diagnosis and management of dyslipidaemia and to prevention of smoking in these patients.

11. In patients with microalbuminuria, the presence of all long term complications of diabetes, especially retinopathy, should be suspected and actively sought.

MICROALBUMINURIA IN DIABETES

Microalbuminuria was first defined in 1982 by the Guys Hospital Group and referred to a subclinical increase in urine albumin excretion in insulin-dependent diabetics which strongly predicted the subsequent development of overt diabetic nephropathy. [1,2] Microalbuminuria was soon after reported to, predict clinical proteinuria and early mortality in non-insulin-dependent diabetics also. [3]

Urine albumin concentration and excretion rate (AER) have been measured in spot and timed specimens by radioimmunoassay for over 20 years, and more recently by semiquantitive screening "dipstick tests". AER in the normal and elevated range has been extensively studied in insulin-dependent diabetics, and to a lesser degree in non-insulin-dependent diabetics, patients with essential hypertension, cardiovascular disease and other renal diseases. Mean AER in normal healthy normotensive patients up to middle-age is 5µg/min or 7.5mg/24hr and rarely exceeds 15µg/min. [4] However, increased AER may occur in hypertension and cardiovascular disease in the elderly especially. [5] Microalbuminuria by consensus is defined as a AER of 20-200 µg/min (corresponding to 30-300 mg/24hr). The upper limit, which defines clinical proteinuria is arbitrary as it can be detected by the "Albustix" reagent strip. There may be variability due to posture, exercise and other factors. [7] As the increase in AER above normal in diabetics is so strongly linked to the eventual development of overt nephropathy (in at least 80% of cases) albeit over many years, it is argued that a raised AER should be labelled incipient diabetic nephropathy. [8]

MICROALBUMINURIA IN TYPE I DIABETES

The prevalence of microalbuminuria in patients with insulin-dependent diabetes has been extensively reported in clinic populations. A prevalence of 22% was found in a large Danish clinic group with type I diabetes for over five years, with a further 19% having microalbuminuria, and a correlation found between albuminuria and hypertension, retinopathy and neuropathy. [9] Another large clinic based study of type I diabetic patients from Denmark excluded hypertensive patients but still found 23% with raised AER. [10] However, the prevalence of microalbuminuria in another clinic sample of normotensive type 1 diabetes was only 12.2%, although the presence of microalbuminuria correlated with diastolic blood pressure. [11] A population-based study found a prevalence of microalbuminuria of 21.2%, correlating with blood pressure and HbA1C. [12] The same relationship between AER and HbA1C was found in a clinic study of type I diabetic patients, with a prevalence of raised AER of 26%. [13] The Pittsburgh Epidemiology of Diabetes Complications study found a combined prevalence of nephropathy and microalbuminuria in diabetes over 30 years duration 84% for males and 59% for females. [14] Microalbuminuria was detected in 31%, and macroalbuminuria in 7% of a large sample of Israeli Type 1 diabetics, with an increased association with patients of non-Ashkenazic (European) origin. [15] In Australia, clinic-based surveys have generally found the prevalence of raised AER in type 1 diabetics to be 20-30%.

MICROALBUMINURIA IN TYPE II DIABETES

Studies comparing the prevalence of microalbuminuria in non-insulin dependent diabetic patients show important differences between non-European and European populations. In a large Danish clinic of type 2 diabetic, raised AER was found in 12.5% of patients,[3] while an equally large Danish type II diabetic cohort had a prevalence of microalbuminuria of 27.1%, macroalbuminuria of 13.5%, and a correlation between albuminuria, blood pressure and coronary heart disease.[16] In a large community diabetic population of type 1 and type 2 patients from Poole U.K., a raised AER and albumin/creatinine ratio was found in 30%, although only 7% showed a AER over 30µg/min.[17] An epidemiological survey of elderly subjects found a wide range of albumin excretion, and an increased albuminuria in both sexes with known type II diabetes.[18] A very large Italian population-based survey of type II diabetic patients found an overall prevalence of microalbuminuria of 25.8%, but only 3% for macroalbuminuria, suggesting a slow rate of progression to clinical proteinuria.[19] Compared to Europeans, Pima Indians have a high prevalence of albuminuria, with 8% of non-diabetics, 15% with impaired glucose tolerance test and 47% of diabetics having a raised albumin/creatinine ratio, which remained a strong predictor for overt nephropathy.[20] Nauruans are even more likely to have albuminuria with 26% of non-diabetics, 43% with impaired glucose tolerance test and 75% of diabetic subjects having at least microalbuminuria. AER correlated with blood pressure but not with diabetes duration.[21] Chinese patients with type II diabetes may also have a high prevalence of albuminuria with a raised albumin/creatinine ratio in 68.8% in one clinic-based report.[22] An outpatient cross-sectional study of type II diabetes in Japan found a prevalence of microalbuminuria of 26%, similar to European reports, with 15% having macroalbuminuria.[23] The prevalence of microalbuminuria is significantly higher in Mexican-Americans, than in non-Hispanic whites, even after adjusting for other variables.[24] A raised AER was found in 26.6% of type II diabetes patients in an outpatient clinic in Northern India [25] and similarly in 28.5% from a group of type II diabetic patients in Southern India.[26] A Guys Hospital study found that British Indians, a group highly susceptible to type II diabetes, were found to have an albumin/creatinine ratio significantly higher than Europid diabetics, and correlating with blood pressure.[27] Diabetes secondary to pancreatic disease represents a non-genetic model of type 1 diabetes. In a group of 86 patients with pancreatic disease and diabetes, microalbuminuria was found in 29%, and AER correlated with duration of diabetes and blood pressure. Although half the subjects had a family history of diabetes, this fact did not influence the albumin excretion rate.[28]

In summary, the prevalence of microalbuminuria, as defined, is remarkably constant in clinic and population surveys of patients with type I diabetes in Australia, Europe and the U.S.A. Prevalence rates of 20-30% are reported, and are not related to duration of diabetes, after ten years, but usually closely correlate to blood pressure. In European populations, the prevalence of a raised urinary albumin excretion in type II diabetes is usually reported as less than for type I diabetes, and also may be related to cardiovascular disease and hypertension as well as diabetes. However, in populations with a high

risk of type II diabetes, a high prevalence of microalbuminuria is noted, even in subjects with impaired and normal glucose tolerance.

COMPARISON OF MICROALBUMINURIA IN IDDM AND NIDDM

Most studies of microalbuminuria have been performed in type I diabetic patients, although the first documentation of microalbuminuria in 1969 related to newly diagnosed patients with type II diabetes.[29] Microalbuminuria in type II diabetes occurs with the same frequency as in type I diabetes.[30,31] However, in up to 30% of type II diabetic patients with microalbuminuria the underlying cause may be of non-diabetic origin.[32,33] Disorders causing non-diabetic microalbuminuria include urinary tract infection, cardiac failure, glomerulonephritis, and essential hypertension.

The presence of persistent microalbuminuria in type I diabetic patients predicts the onset of diabetic nephropathy after an interval of 5-15 years. By contrast, persistent microalbuminuria in the type II diabetic patient mainly predicts cardiovascular mortality [34,3] and has been reported to lead to clinical nephropathy to a much lesser degree.[35] A contrary view has been expressed by two other groups.[36,37] In Australia the overall incidence of diabetic nephropathy presenting to dialysis and transplant centres has increased in both absolute and relative terms from 1985 to 1990 (1985, 50 patients, 8% of total; 1990, 135 patients, 14% of total).[38] Approximately equal numbers of type I and type II diabetic patients are treated at end-stage renal failure centres. Whether this represents a true reflection of the incidence of diabetic nephropathy or a selection bias favouring type I diabetic patients is not yet clear. In New Zealand, diabetic renal failure was the most common cause of renal disease for acceptance to dialysis and transplant centres in 1990. This reflected a recent increase in the number of Maori and Pacific Islanders, and elderly type II Caucasoid diabetics.[38]

MICRO VERSUS MACROALBUMINURIA

Macroalbuminuria is conventionally equated with clinically overt diabetic nephropathy. It is defined as an albumin excretion rate of over 200µg/min and is equivalent to a total daily protein excretion of greater than 0.5G. Several longitudinal studies have demonstrated that persistent microalbuminuria indicates an approximately 20 fold increase in risk for the development of nephropathy, and 70-80% of microalbuminuric patients with type I diabetes go on to develop nephropathy.[2,39,40,41]

Once persistent macroalbuminuria has developed, there is a progressive decline in renal function and the process is generally regarded as irreversible.[42,43,44,45] The rate of fall of glomerular filtration rate varies approximately five fold and is more rapid in patients with hypertension.[46] High dietary protein intake may also increase the rate of decline of renal function. However, improved glycaemic control has not been shown to modify the rate of decline of renal function in macroalbuminuric diabetic patients, in contrast to its effects in microalbuminuric patients.[47] Persistent microalbuminuria and macroalbuminuria in diabetic patients are associated with increased risk not only for renal disease but also for proliferative retinopathy and cardiovascular morbidity and mortality.[48] The high relative mortality from cardiovascular

disease in diabetics with both microalbuminuria [49] and macroalbuminuria [50] indicates a strong association between diabetic microangiopathy and macroangiopathy.

MICROALBUMINURIA AND RENAL BIOPSY

Renal biopsy is indicated in diabetic patients with proteinuria who show features which are not characteristic of diabetic nephropathy. These include the presence of persistent proteinuria in the first 10 years of type I diabetes [33] and the absence of retinopathy.[9] The presence of red cells, and especially red cell casts, has been considered to be an indication of non-diabetic renal disease, [51] but other investigators have found that haematuria is not helpful in separating diabetic and non-diabetic renal disease. [52]

Although the above indications for renal biopsy have till now applied to patients with macroalbuminuria, it is appropriate to consider the same indications in patients with atypical presentation of persistent microalbuminuria. The histological diagnosis of a non-diabetic renal disorder may provide useful prognostic and, less commonly, therapeutic information. On the basis of current knowledge, the following recommendations have been made for the use of renal biopsy on clinical grounds alone. [53]

Biopsy on Clinical Grounds alone if

a) IDDM <10 year and absence of any diabetic retinopathy with clinical evidence of renal disease

b) NIDDM with clinical renal disease in absence of background or proliferative retinopathy independent of duration

c) if rate of decline of GFR or rise in AER falls outside established norms or when clinical and laboratory findings indicate increased likelihood of non-diabetic renal disease

d) IDDM in whom a multi-system disease (eg systemic lupus) is suspected or present

TESTING PROCEDURES FOR MICROALBUMINURIA

As a consequence of the lack of uniformity in definition of microalbuminuria between group comparisons are difficult. Measurement of albumin excretion rate (AER) in a timid urine collection should be regarded as the gold standard for the definition of microalbuminuria. [6] However, timed urine collections are cumbersome for patients and laboratory staff, subject to inaccuracies of timing and completeness and associated with poor compliance unless part of the patients usual clinical routine. [54] Alternative screening procedures include first voided early morning urine (EMU) or random urine specimens.

RANDOM URINE SPECIMENS

Data from the Poole survey of 313 diabetic subjects [55] shows a correlation between random UAC and AER by timed overnight collection of only 0.45. Using a urinary albumin concentration > 15 µg/ml to predict AER> 30 µg/min, the sensitivity was 75%, specificity 73% and positive predictive value 18%. If a higher urinary albumin of >25µg/ml is used sensitivity falls to 56% with specificity rising to 81%. Other studies have demonstrated correlation coefficients of 0.32-0.68. [56] Because of the low specificity of random UAC the resultant large number of false positives may result patient anxiety and considerable numbers of repeat tests or timed urine collections needing to be performed. Little improvement may be obtained by using albumin:creatinine ratio in random urine specimens. Using an albumin:creatinine ratio >3.4 mg/mmol Wiegmann et al [57] found a sensitivity of 82% and specificity of 81% in identifying AER > µg/min in a 24 hour collection. Similar results of 80%, 81% and 20% for sensitivity, specificity and positive predictive value respectively were obtained by Gatling et al. in the Poole survey for albumin:creatinine ratio >3.0mg/mmol identifying AER >30 µg/min. [55] However, more optimistic results have been obtained by Watts et al [58] who report a sensitivity of 100% and specificity of 96% for albumin:creatinine ratio > 8.0mg/mmol predicting AER > 30µg/min.

EARLY MORNING URINE

The correlation between urinary albumin concentration in a first voided urine and AER in both timed overnight and 24 hour urine collections is much greater than with random urine specimens (r = 0.86- 0.90). [55,59] In most studies sensitivity and in particular specificity improve substantially with early morning urine specimens along with some modest further gain in these parameters if albumin:creatinine ratio is used. Although measurement of creatinine would result in more expense more studies have been published using albumin:creatinine ratio. The major problem involves choosing an appropriate cut-off level.

The European St Vincent declaration for the prevention of diabetic renal disease [60] suggests the following approach:

1. Albumin:creatinine ratio <2.5 mg/mmol in men and <3.5mg/mmol in women or albumin conc. <20 mg/l). Considered normal, retested yearly.

2. Albumin;creatinine ratio ≥ 2.5mg/mmol in men and ≥3.5mg mmol in women or albumin conc. ≥ 20mg/l). Timed urine collection needed. If this is abnormal, that is, AER >20µg/min, then 2 additional samples should be tested within 6 weeks to confirm the diagnosis of persistent microalbuminuria If one of the 3 timed urine collections reveals AER <20 µg/min the patient may be considered normoalbuminuric and retested annually.

3. If 2 or more timed urine collections reveal AER >20µg/min the patient is considered to have persistent microalbuminuria.

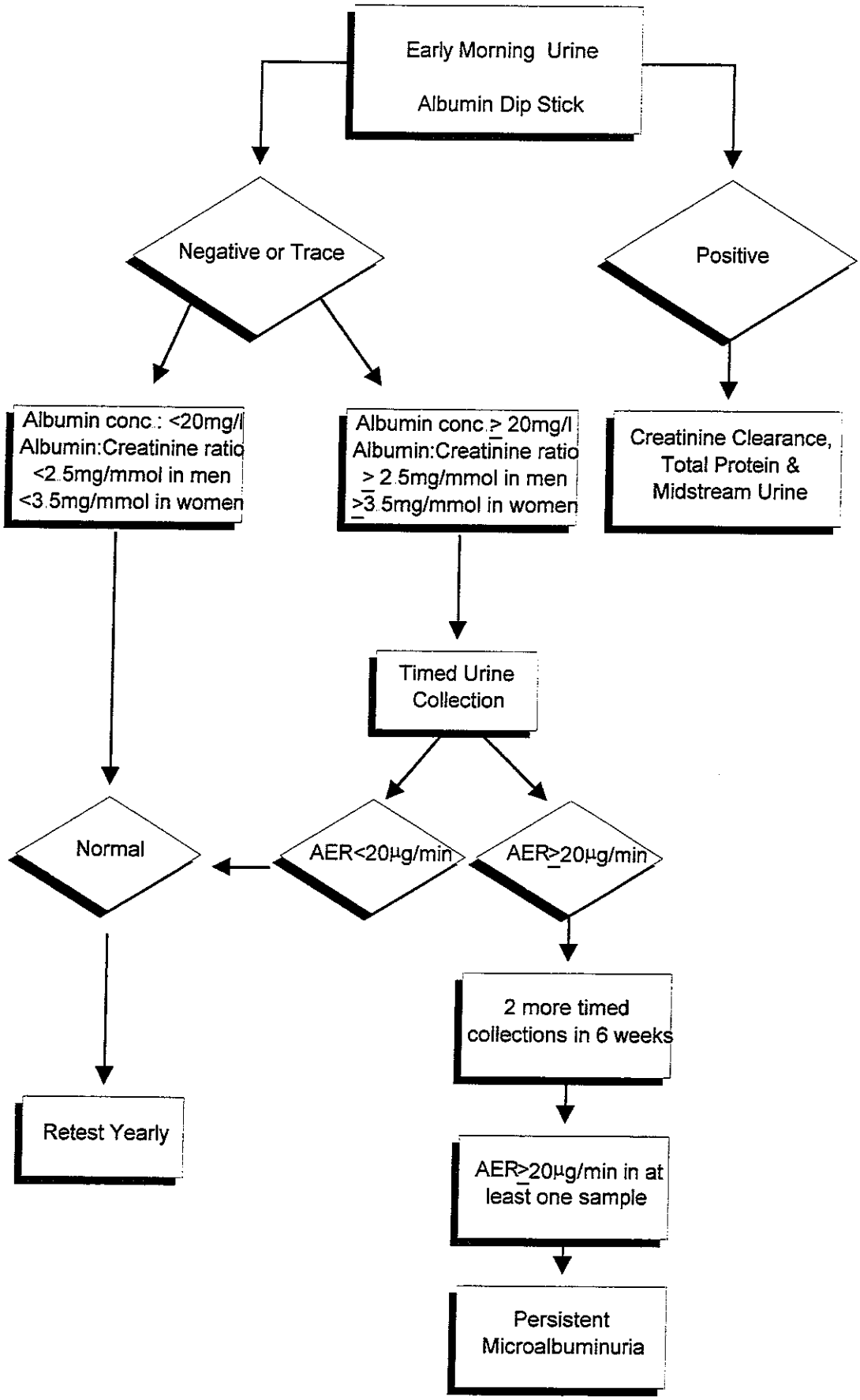
DIPSTICK DETECTION OF MICROALBUMINURIA

Micral-Test (Boehringer Mannheim, GmbH Mannheim, Germany) is an immunochemically based urinary dipstick for the semi-quantitative determination of microalbuminuria. No studies have been published which examine the usefulness of Micral-Test strips in random or early morning urine specimens in predicting microalbuminuria as assessed by timed urine collections. According to a recent study of 298 consecutive 24 hour collections performed in diabetic subjects, [61] when compared with RIA a Micral-Test result of $\geq$ 20mg/l had a sensitivity of 92.2%, specificity of 92.3% and positive predictive value of 37.8% in predicting an AER $\geq$ 20 µg/min.

RECOMMENDATIONS FOR SCREENING

Due to the cumbersome nature of timed collections and variability of AER in random urine collections we propose that the first voided early morning urine specimen be used for initial screening. Patients could be given a standard 50 ml urine container which they use to collect a first voided early morning urine specimen bringing this specimen to their next attendance at the clinic (morning or afternoon). Testing of the urine may be done by either of two protocols: one using Micral-test and the other using albumin:creatinine ratio as the initial screening test - Figure 1.

Figure 1.


Early Morning Urine
Albumin Dip Stick
Negative or Trace
Positive
Albumin conc.: <20mg/l
Albumin:Creatinine ratio
<2.5mg/mmol in men
<3.5mg/mmol in women
Albumin conc.≥ 20mg/l
Albumin:Creatinine ratio
> 2.5mg/mmol in men
≥3.5mg/mmol in women
Creatinine Clearance,
Total Protein &
Midstream Urine
Timed Urine
Collection
Normal
AER<20µg/min
AER≥20µg/min
2 more timed
collections in 6 weeks
Retest Yearly
AER≥20µg/min in at
least one sample
Persistent
Microalbuminuria

MANAGEMENT OF MICROALBUMINURIA - ANTIHYPERTENSIVE AGENTS

Microalbuminuria is commonly associated with a modest rise in blood pressure and therefore the role of antihypertensive therapy has been evaluated in this condition. The role of antihypertensive therapy has been considered in both the hypertensive and normotensive patient with microalbuminuria. Most studies have concentrated on the insulin-dependent diabetic patient, although more recently the role of these agents in the non-insulin dependent diabetic has also been considered. Hypertension generally does not develop in insulin dependent diabetic subjects until the onset of overt clinical nephropathy. [62] Furthermore, prospective studies have suggested that the blood pressure gradually rises as the patients develop persistent proteinuria. [63] It has been shown that hypertension is associated in these patients with early onset of renal impairment. [46] The importance of blood pressure in microabluminuric subjects has been recently emphasised by cross-sectional studies which revealed that patients with microalbuminuria had higher blood pressure that subjects with normal urine albumin excretion, when matched for age and duration of diabetes. [64]

In non-insulin dependent diabetes, hypertension has also been associated with microalbuminuria although the situation is much more complex since hypertension is commonly associated with non-insulin dependent diabetes independent of the presence of albuminuria or nephropathy. [65] More recently, experimental studies have been performed which have revealed the importance of hypertension, in the genesis of nephropathy. [66] Furthermore, in both hypertensive and normotensive situations various anti-hypertensive agents have been administered to diabetic animals and shown to prevent the development of both functional and structural markers of nephropathy. These results have been the impetus for extensive investigation of anti-antihypertensive therapy in both normotensive and hypertensive microalbuminuric subjects.

BLOOD PRESSURE LOWERING THERAPY IN THE HYPERTENSIVE DIABETIC PATIENT

Initial studies were performed in the early 80's using the beta blocker, metoprolol. [67] This agent reduced albuminuria by 50% and the effect was similar to findings that had previously been reported in subjects with established nephropathy. More recent studies using the ACE inhibitor, perindopril, have shown similar effects, as has the agent indapaide in a group of microalbuminuric, non-insulin dependent diabetic patients with hypertension. The recent Melbourne Diabetic Nephropathy Study revealed similar findings in which hypertensive micoalbuminuric subjects with either type I or type II diabetes had a reduction in urinary excretion if they were treated with either perindopril or the calcium antagonist nifedipine. [68]

A similar result in a short-term study using enalapril and nicardipine was seen in hypertensive microalbuminuric non-insulin dependent diabetic patients. [69] Thus, all studies in microalbuminuric subjects with hypertension which have shown a significant reduction in urinary albumin excretion with effective blood pressure lowering therapy. Furthermore, the class of antihypertensive agent

does not appear to be important. The mainstay of therapy in hypertensive, microalbuminuric patients should be reduction in elevated blood pressure. The end point for blood pressure reduction remains to be ascertained with no lower limit of blood pressure as yet having been determined. It is still not clear if a reduction in urinary albumin excretion is associated with any significant improvement in renal function since microalbuminuria is generally associated with normal or elevated glomerular filtration rate. However, if one extrapolates from the data that have been obtained from patients with established nephropathy it appears likely that reductions in urinary albumin excretion will be associated with a retardation or prevention in decline of glomerular infiltration rate and preservation of renal function.

USE OF ANTI-HYPERTENSIVE AGENTS IN NORMOTENSIVE PATIENTS WITH ESTABLISHED MICROALBUMINURIA

Treatment of the normotensive patient with microalbuminuria with antihypertensive agents remains a clinical dilemma. The study by Marre et al confirmed that in the normotensive patient enalapril, when compared to placebo, was more effective in reducing urinary albumin excretion.[70] Although the effects on urinary albumin excretion were modest the natural history of this condition as observed in the placebo group revealed a progressive increase in urinary albumin excretion over a twelve month period. Several other studies have confirmed that rises in albuminuria are at least prevented if not reduced in both the short-term and the long-term with angiotensin enzyme inhibitors.[68,71]

These findings were confirmed in a more recent four year prospective study in which captopril reduced urinary albumin excretion whereas placebo was associated with a progressive rise in urinary albumin excretion. The authors concluded that ACE inhibition postponed the development of macroalbuminuria.[72] At this state, it is not clear if this reduction in urinary albumin excretion will ultimately be translated to prevention or retardation of the development of renal failure.

The role of non-ACE inhibitors in the treatment of microalbuminuria remains to be ascertained. The Melbourne Diabetic Nephropathy Study suggested that the calcium antagonist, nifedipine, prevented a rise in albuminuria but did not reduce urinary albumin excretion in normotensive microalbuminuric insulin and non-insulin dependent diabetic patients. Furthermore, a short-term study by Mimran et al[71] suggested an increase in urinary albumin excretion in such subjects, although this has not been a uniform finding. More recently, a study by Hallab et al.[70] has suggested that ACE inhibitors may be more effective than hydrochlorothiazide in reducing urinary albumin excretion in normotensive microalbuminuric type I diabetic patients despite equivalent reduction in blood pressure. Therefore, at this stage one can conclude that ACE inhibitors are effective in preventing the rise in urinary albumin excretion and may decrease urinary albumin excretion in insulin dependent diabetic patients with microalbuminuria. The role of other antihypertensive agents remains to be ascertained. In non-insulin dependent diabetes the issue is much less clear and remains an area of controversy.

TREATMENT OF MICROALBUMINURIA - NON-ANTIHYPERTENSIVE THERAPY

In patients with established microabluminuria it remains to be determined if other agents should also be considered. There is a large class of new agents that may prevent diabetic renal complications and these remain at this stage purely in the research area. Such agents include aldose reductase inhibitors, inhibitors of prostaglandin and thromboxane synthesis and aminoguanidine, an inhibitor of advanced glycation. The major issues at this state relate to the role of improved glycaemic control and reduced protein intake. The recent re-evaluation of the Steno study [73] in which intensified insulin therapy achieving improved glycemic control but not normoglycemia was compared to conventional insulin therapy suggests that in the microalbuminuric phase there was some benefit of intensified insulin therapy. Although the evidence was not initially very clear at the 24 month analysis point, [74] more recent data suggest that intensified insulin therapy is associated with a reduced rate of progression of microalbuminuria. If one can avoid the complications of intensified insulin therapy, especially an increased hypoglycaemia, then improving diabetic control appears to be an important part of the treatment of the patient with established microalbuminuria. A definitive answer to the issue of improved glycemic control and the management of microalbuminuria has been recently provided by the results of the Diabetes Control and Complication Trial. [75]. This trial showed, at least for retinopathy, that the lower the glycated haemoglobin concentration the lower the risk. Similar results were obtained for the risk of progression to incipient or overt nephropathy, using albumin excretion as the endpoint, and the general conclusion was that any improvement in glycaemic control is worthwhile and each patient should be helped to achieve the best possible control. Reduced protein intake appears to be an effective way of reducing urinary albumin excretion even in the setting of microalbuminuria. [76] Its relevance to the ultimate postponement of end stage renal failure in this clinical situation has not been clearly proven and it is well known that the degree of protein restriction that has been shown to reduce urinary albumin excretion may be too severe for some patients.

Therefore, the role of protein restriction remains a secondary aspect of management of the diabetic patient with established microalbuminuria.

ROLE OF GLOMERULAR FILTRATION RATE MEASUREMENT IN DIABETIC MICROALBUMINURIA

During the first few years of diabetes, and in the early microalbuminuric period, hyperfiltration occurs in 20-25% of patients [77,78] under conditions of usual glycaemic control. If there is a marked improvement in glycaemic control (HbA1C < 7.5%) which is sustained for 3 months or more, the glomerular filtration rate tends to fall to normal levels. [79] As the albumin excretion rate increases into the "high" microalbuminuric range, GFR begins to decline, and this decline accelerates as macroproteinuria develops. Thus, a falling GFR in a microalbuminuric may represent normalization of hyperfiltration, or a true decline in renal function, and must therefore be interpreted with caution.

It is now well established that treatment of hypertension has a beneficial effect on the progression of diabetic nephropathy.[80,81] These studies have not only shown a reduction in the rate of progression of albuminuria, but also a slowing in the rate of decline of renal function. Similar findings have been reported in normotensive diabetic patients,[70] where the ACE inhibitor enalapril reduced the rate of decline of GFR form 15%/year to 5%/year. Thus, accurate GFR measurements can provide some indication of the efficacy of a particular treatment in slowing the progression of diabetic nephropathy. There is some evidence to suggest that hyperfiltration may be a causative factor in the development of microalbuminuria and subsequent diabetic nephropathy. Mogensen[82] studied 12 patients who had GFR measurements performed over a long period of time, and found that those who developed albuminuria at follow up had initially exhibited an elevated GFR. Furthermore, the subjects who initially hyperfiltered all showed a significant decline in GFR, and two developed renal failure. Another study found that elevation of GFR (>125ml/min), had a 51% positive predictive value for the development of nephropathy over 8 years, and a GFR <125ml/min had a 95% negative predicitve value.[83] However, two other studies over 8 years,[84] and 18 years[85] of follow up have failed to demonstrate such a relationship.

Accurate GFR measurements (eg. isotopic methods using DTPA, CrEDTA, Iothalamate, etc) performed at regular intervals, will assist in determining the significance of any changes in renal function which occur in diabetic patients. In early diabetes, an elevated GFR would be possible marker of problems in the future, and these patients could be followed carefully for the development of nephropathy and elevated BP treated vigorously. In the microalbuminuric stage, a falling GFR should be a possible indicator of declining renal function, or may be due to reversal of hyperfiltration, and frequent measurements should be performed. However, GFR which continues to decline to below normal levels is very suggestive of impending renal failure, and aggressive treatment should be instituted.

Currently, the methods for measuring GFR isotopically are not available in all centres, and reproducibility is a problem in some centres. Therefore, the role of routine GFR measurements in standard clinical practice requires further evaluation, particularly during the early phases of diabetic nephropathy.

COST EFFECTIVENESS OF TREATING MICROALBUMINURIA

Microalbuminuria is a strong predictor of overt diabetic nephropathy, the end result of which is end stage renal failure. The cost of a patient developing this condition is considerable, and cannot be measured solely in economic terms. Chronic renal failure requiring dialysis (if indeed a patient is accepted for dialysis) makes a major impact on a patient's health, quality of life, and earning ability. This analysis will concentrate on the economic cost of offering dialysis to patients with chronic renal failure.

Renal dialysis currently costs between $28,000 and $37,000 per year, depending on whether home or hospital based services are used.[86] The survival of patients entering dialysis programs varies, depending on the

underlying disease, but is at least 80% at 5 years for those subjects who would be eligible for transplantation. Thus, taking an average cost of around $30,000 per year, management of a patient accepted onto a dialysis program will cost between $150,000 and 300,000 depending on survival time on dialysis.

There are approximately 42,000 new cases of diabetes diagnosed each year in Australia. [87] Of these, approximately 4000 will have Type I diabetes. Since the incidence of renal failure in Type II diabetes is currently uncertain, the analysis will concentrate on type I diabetes.

Approximately 25-30% of type I diabetic patients will be expected to develop diabetic nephropathy. This represents 1,260 patients/year. If all of these were accepted for dialysis, the cost would be 1260 x 5 years x $30,000/year = $189,000,000/year, assuming a 5 year survival, for type I diabetic patients alone. However, at present only 135 diabetic patients are accepted for dialysis each year, [88] representing a cost of 20 million dollars/year. The dialysis acceptance rate for new diabetic patients is steadily increasing, and this fact, combined with the steadily increasing incidence of Type II diabetes, means this cost will steadily rise.

If treating microalbuminuria with an ACE inhibitor can slow the onset of diabetic nephropathy, the cost benefit of treatment may be significant. The presence of microalbuminuria has approximately an 80% power of predicting diabetic nephropathy over 10 years. The calculations in the table assume a 10 year interval before dialysis commences.

The cost of ACE inhibitor therapy is approximately $360/year. Since hypertensive patients are already taking antihypertensive drugs, this cost is only relevant in normotensive patients

The present value in the table represents the costs valued back to 1993 dollars. Thus, they do not and should not include any component for inflation. The basic assumption for these calculations is that deferral of a cost represents a saving which can be estimated in current dollar terms.

Three scenarios are represented:

1. No ACE inhibitor is used, dialysis commences in 10 years and the patient survives 8 years on dialysis.

2. ACE inhibitor is used, dialysis is deferred 5 years and the patient survives 5 years on dialysis.

3. ACE inhibitor is used, dialysis is deferred 5 years and the patient survives 5 years on dialysis. The data suggest that the treatment of microalbuminuria with an ACE inhibitor will be cost effective providing the onset of renal failure can be deferred by an average of 2 years. If renal failure can be prevented entirely, the savings will be much greater.

Recent studies in the United States and Europe have examined cost-effectiveness of screening and early treatment of diabetic nephropathy in patients with insulin-dependent diabetes mellitus [89,90]. The cost estimates were based on the use of an angiotensin converting enzyme inhibitor in all insulin dependent diabetic patients who developed persistent microalbuminuria. A conservative assumption on the delay of progression of nephropathy by 50% yielded a theoretical cost of $16,494(US) per year of life saved. An optimistic assumption on the delay of progression of nephropathy by 75% yielded a cost of $7,935(US) per year of life saved. For instance, initiating treatment with an ACE inhibitor in patients with type I diabetes and microalbuminuria may be expected to increase median life expectancy by 4 to 14 years and reduce the need for dialysis transplantation by 21-63% [91]. It must be emphasised that these estimates hinge on the effectiveness of angiotensin converting enzyme inhibitors on the course of early nephropathy. In particular, clinical trials are needed to confirm that a treatment-induced delay in progression of albuminuria is coupled with a delay in onset of a decline in glomerular filtration rate. Also, cost effectiveness estimates need to take into account the recently described decrease in predictive value of microalbuminuria in patients with greater than 15 years duration of insulin-dependent diabetes.[91]

PRESENT VALUE COSTS AND BENEFITS OF TREATING MICROALBUMINURIC DIABETIC PATIENTS WITH ACE INHIBITION

	Scenario 1 No ACE inhibitor Dialysis commences 2003, for 8 years		**Scenario 2** ACE inhibitor used Dialysis deferred 2 years and continues 8 years		**Scenario 3** ACE inhibitor used Dialysis deferred 5 years and continues 5 years	
Year	Cost*	discount @ 5% PV 1993#	Cost*	discount @ 5% PV 1993#	Cost*	discount @ 5% PV 1993#
1993			360	360	360	360
1994			360	342	360	342
1995			360	325	360	325
1996			360	309	360	309
1997			360	293	360	293
1998			360	279	360	279
1999			360	265	360	265
2000			360	251	360	251
2001			360	239	360	239
2002			360	227	360	227
2003	30,000	11,975	360	216	360	216
2004	30,000	11,376	360	205	360	205
2005	30,000	10,807	30,000	10,807	360	195
2006	30,000	10,267	30,000	10,267	360	185
2007	30,000	9,753	30,000	9,753	360	176
2008	30,000	9,266	30,000	9,266	30,000	9,266
2009	30,000	8,803	30,000	8,803	30,000	8,803
2010	30,000	8,362	30,000	8,362	30,000	8,362
2011			30,000	7,944	30,000	7,944
2012			30,000	7,547	30,000	7,547
Total present value cost at 1993 ($1993)		**$80,609**		**$76,059**		**$45,786**
Savings per patient ($1993)				**$4,550**		**$34,823**

* Cost in 1993 dollars for dialysis assumed to be $30,000 (in reality it is possible [1] the real resource cost of dialysis may be expected to fall over the next decade), and for ACE inhibitor at $30 per month.

\# Cost of dialysis or ACE inhibitor in 1993 dollars present valued to 1993, to reflect the fact that a cost incurred sooner rather than later represents a greater burden. Obtaining a present value estimate is a way of comparing cost (and benefit) streams that occur over different time frames. A 5% social rate of discount is widely accepted as representing a suitable discount rate to use for the purpose of calculating present value.