Microalbuminuria and Early Diabetic Nephropathy:

Where Have All The Patients Gone?

Julio Rosenstock, M.D.
Medical Ground Rounds

University of Texas Southwestern Medical Center at Dallas
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I. INTRODUCTION

End stage renal failure secondary to diabetes mellitus is an increasing health and socioeconomic problem in the United States. Twenty five to thirty percent of all patients beginning dialysis therapy for end stage renal disease in this country have diabetic nephropathy. By the end of this decade, the cost of care for the uremic diabetic patient is estimated to approach 2 billion dollars a year.

Once diabetic nephropathy becomes manifest, attempts to halt the relentless progression of the disease have been essentially unsuccessful. It appears that when diabetic nephropathy reaches a certain level of severity, the process becomes self perpetuating. When this stage is reached, improvements in glycemic control have not been demonstrated to have any obvious beneficial effect, and only antihypertensive treatment seems to retard the progression of the kidney disease.

Recent reports claim to have identified an earlier stage of diabetic nephropathy characterized by a persistent elevation of urinary albumin excretion rate in otherwise healthy non proteinuric diabetic subjects. The suggestion has been made that persistent microalbuminuria is predictive of future development of overt diabetic nephropathy.

In today's rounds I will address the issue of diabetic nephropathy from the different and hopefully more promising perspective of early identification and early intervention. Microalbuminuria, a whether "predictor of future diabetic nephropathy" or rather, just a "marker of incipient hypertension", seems amenable to therapeutic interventions that can perhaps alter the course of diabetic renal disease.

II. OVERT DIABETIC NEPHROPATHY

1. <u>The Magnitude of the Problem:</u>

Diabetic nephropathy is the single most common cause of renal failure in the United States accounting for nearly one third of all patients enrolled in the medicare end stage renal disease program (1). Table 1 summarizes data emanated from the Health Care Financing Administration, revealing the magnitude of the problem involved in diabetic nephropathy (2). It has been estimated that the cost of a kidney transplant for the first year is approximately $30,000 for a LRT and $40,000 for a CRT (3). Providing that the patient has a functioning graft, the subsequent annual costs are $5,000 for a LRT, and $7,000 for a CRT. The costs of a hemodialysis patient is approximately

$25,000 to $30,000 per year. Overall, patients stay on dialysis an average of 5 years, but survival in the program for diabetic patients is shorter, around 3 years, because of the increased cardiovascular morbidity and mortality (4). The socioeconomic burden on the national health care costs imposed by the diabetic renal disease is so substantial that it has dwarfed the initial estimate of $2 billion a year by the end of this decade (5).

Table 1 (From Ref 2)

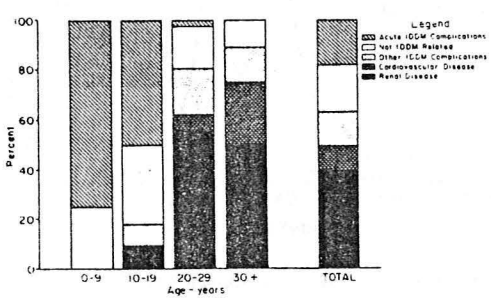
THE COST OF DIABETIC NEPHROPATHY

HCFA 1986 Data

- 90,000 dialysis patients in ESRD medicare program
- 30,000 new patients began dialysis
- 9,000 patients received kidney transplants
- 30% of all dialysis patients have diabetic nephropathy
- If 2% annual increase rate persists, by the next decade, diabetic nephropathy will account for 50% of all ESRD
- Mortality remains high, more than 15,000 patients died in 1986

The Pittsburgh insulin-dependent diabetes mellitus morbidity and mortality study analyzed 1,894 patients with insulin-dependent diabetes diagnosed between 1950 and 1981 (6). Overall, IDDM patients had a sevenfold excess in mortality risk compared with the U.S. population of the same age. The average age of death in 8.7% of this population was 23 years. The magnitude of the increased mortality was particularly striking among patients 25-40 years of age. More than 2% of these patients died each year, which is nearly a 20 fold greater mortality compared with the U.S. population. In this age group, (25-40 years), renal disease accounted for more than one half of all the deaths (Fig 1).

Figure 1 (From Ref 6)

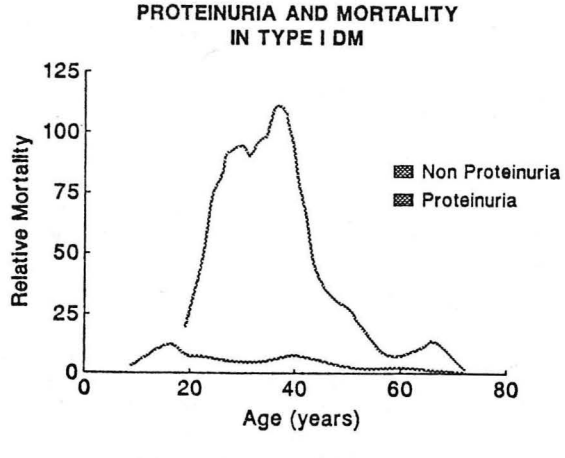


Distribution of causes of death by age at death.

Diabetic nephropathy is the major cause of death in Type I diabetes mellitus. Deckert et al, reported that of patients whose illness was diagnosed before the age of thirty-one and analyzed after at least 40 years of diabetes, proteinuria was present in 38% and uremia in 22% of the patients (7). The excess mortality among patients exhibiting persistent proteinuria with less than 40 years of diabetes was 3-4 times higher than in those patients, who after 40 years of diabetes were free of proteinuria.

Subsequent studies from the Steno Memorial Hospital in Denmark indicate that after 40 years of diabetes, only 10% of the patients who developed nephropathy were alive, whereas >70% of patients who did not develop nephropathy survived. Uremia was the cause of death in 66% of the patients with nephropathy. The mortality rate was around 49% in patients who had persistent proteinuria for seven years (8). More recently, they reported the effects of proteinuria on relative mortality in 1,134 Type I insulin-dependent diabetic patients diagnosed between 1933 and 1952 who were followed until 1982 or death (9). Relative mortality was defined as the observed number of deaths given the age, sex and calendar year in the diabetic population, divided by the expected number of deaths given the same variables in the non-diabetic population. A steep increase with a maximal relative mortality of nearly 100 fold, was found among patients with persistent proteinuria in the 30-40 year age range (Fig 2). Patients who did not develop proteinuria had a much lower but still 2 fold increased relative mortality. Uremia was the main cause of death in patients with persistent proteinuria. Cardiovascular deaths were also more frequently found in the proteinuric patients.

Figure 2 (From Ref 9)

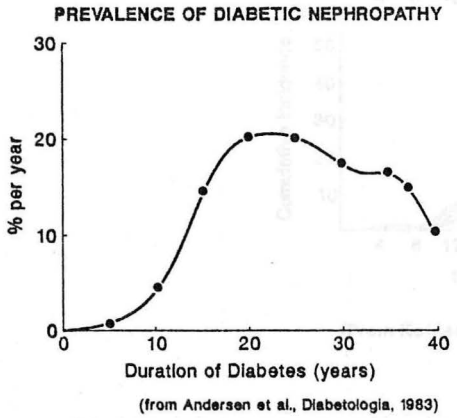


(From Borch-Johnsen et al, Diabetologia, 1985)

2. The Natural Course of Diabetic Nephropathy:

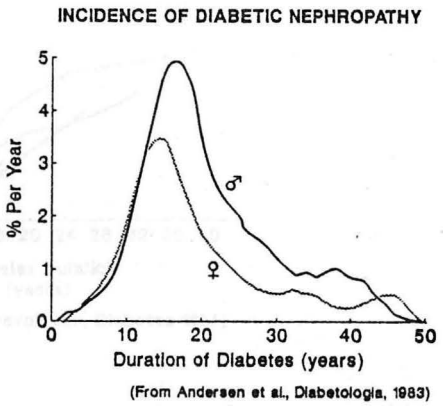
Over the years, very important information on the natural history of diabetic nephropathy has continued to emerge from the series of elegant epidemiological studies carried out at Steno Memorial Hospital. These workers have been able to analyze nearly 25% of all insulin-dependent diabetic patients diagnosed in Denmark between 1923 and 1972. Their initial report was based on 1,303 patients diagnosed between 1923 and 1953 who were followed until death or for at least 25 years after the onset of diabetes (8). Persistent proteinuria as defined by a protein excretion >0.5 g/24h in at least 4 consecutive 24h samples was found in 41% of the patients. Approximately 57% did not develop persistent proteinuria during the follow-up period. The prevalence of nephropathy relative to duration of diabetes is shown in Figure 3. The maximal prevalence of nephropathy in relation of diabetes was 21% after 20-25 years of diabetes. It declined in patients who had suffered from diabetes for 40 years or more. Figure 4 illustrates the original incidence rate of proteinuria. The cumulative incidence data from the study indicate that approximately 45% of all insulin-dependent diabetics will develop nephropathy after 40 years of the disease.

Figure 3 (Ref 8)



(from Andersen et al., Diabetologia, 1983)

Figure 4 (Ref 8)

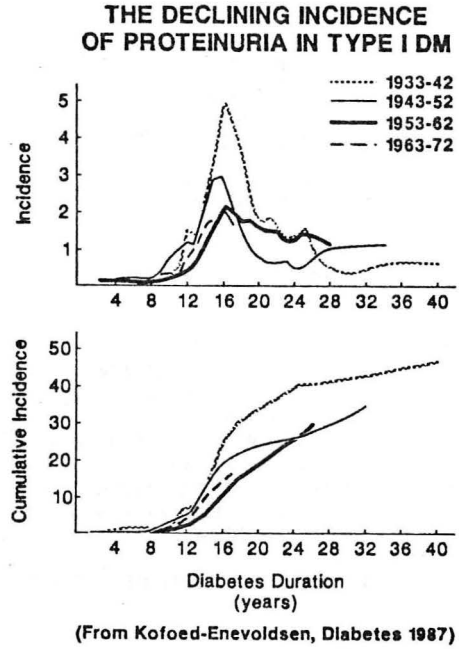


(From Andersen et al., Diabetologia, 1983)

More recently an extensive re-analysis of the Steno population demonstrated a declining incidence of persistent proteinuria in Type I insulin-dependent diabetic patients in Denmark (10). They reviewed the data on 2,658 patients who represented approximately 30% of all Danish insulin-dependent

diabetic patients subjects diagnosed between 1933 and 1972 and followed until January, 1984 or death. When comparing patients diagnosed between 1933 and 1944 with those diagnosed between 1953 and 1962, the incidence of proteinuria decreased by 30%. The peak incidence of proteinuria was found to be around 15-17 years of diabetes duration. This declining incidence resulted in a decrease in cumulative incidence of diabetic nephropathy after 25 years from 41% in patients diagnosed between 1933 and 1942, to 27% in patients diagnosed between 1953 and 1962 (Fig 5). The decreasing incidence of proteinuria may account for the previously reported decline also in relative mortality in Denmark (11). Patients diagnosed of having Type I diabetes after 1956 had a 30-40% lower relative mortality than patients diagnosed from 1933 to 1946.

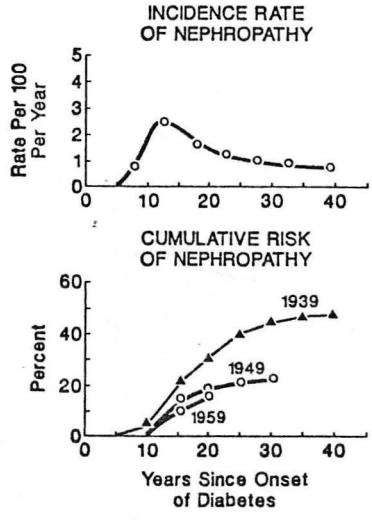
Figure 5 (Ref 10)



Similar data are available from the Joslin Clinic reporting on a cohort of 292 insulin-dependent diabetic patients who were followed for 20 to 40 years (12). Patients diagnosed in the 1930's had double risk of persistent proteinuria as compared to those in whom the diabetes was diagnosed in later decades as shown in Figure 6. The cumulative risk of diabetic nephropathy in patients with Type I diabetes diagnosed in 1959 and 1979 is around half of what is found in those patients with diabetes

diagnosed in 1939 (13). Although lower than previously reported, the overall cumulative risk of developing diabetic nephropathy was 35% after 40 years of diabetes duration.

Figure 6 (Ref 13)



Once clinical proteinuria develops in diabetic patients glomerular function progressively and relentlessly declines. The mean duration of diabetes at the onset of proteinuria and the subsequent clinical course was reported by the Joslin Clinic (14) in a retrospective study that has become classic (Table 2). After the onset of proteinuria, the average survival is 10 years. End stage renal failure develops in approximately 25% of the patients within 6 years, in 50% within 10 years, and in 75% within 16 years (12). Similar results were found at the Steno Hospital in Type I diabetic patients who developed persistent proteinuria after an average duration of 17 years of diabetes and death ensued 5-7 years thereafter (15).

Table 2 (Ref 14) **THE JOSLIN RETROSPECTIVE STUDY**

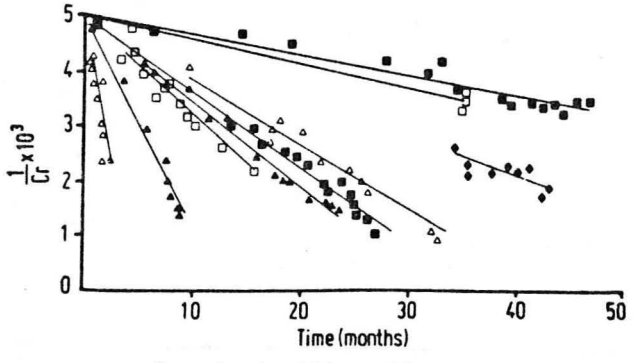
	Onset of Proteinuria (n=112)	Renal Failure Early (n=70)	Renal Failure Late (n=62)	Death (n=61)
Duration of Diabetes (yr)	17.3±6	19.4±5	21.6±6	22.1±6
Serum Creatinine (mg/dl)	1.2±0.3	2.8±0.9	8.5±3	12.4±6

(From Kussman et al, JAMA, 1976)

From a more positive perspective, these epidemiological data indicate that approximately 60-65% of all insulin-dependent diabetic patients are spared from developing nephropathy even after very long term follow-up periods. Furthermore, the Steno and Joslin data show that the risk for overt proteinuria begins after a lag period of 5 years, the incidence rate peaks in the second decade and declines thereafter, suggesting that this complication occurs mainly in a subset of susceptible patients. A very attractive, though speculative interpretation of the decline in the incidence rate after 20-25 years of diabetes is that the pool of genetically susceptible nephropathic patients becomes exhausted over time (13).

The rate of deterioration of glomerular function in diabetic nephropathy varies considerably among patients. However, the decline is linear over time and is characteristic and fairly predictable for the individual patient (16,17). Once the serum creatinine concentration rises above 2 mg/dl, the progression to renal failure in each individual patient is constant and predictable. The relationship between the inverse of the serum creatinine concentration and time in months is used to show this straight line correlation (Fig 7).

Fig 7 (Ref 17).

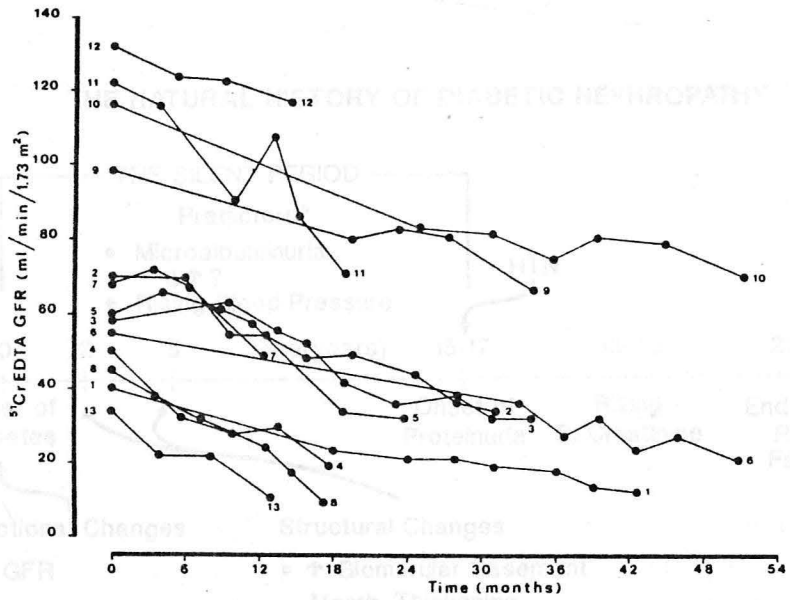


Progression of renal failure in 9 diabetic patients. Inverse of serum creatinine (μmol/L) plotted against time.[25]

Prospective studies in insulin-dependent diabetic patients with clinical proteinuria have also shown that the decline in GFR has a striking linear relationship with time (18,19). Mogensen found that GFR fell at a rate of 0.9 ml/min/month during 34 months of obversation (18). Recently, Viberti et al, (19) reported similar linear decline in GFR. In this study the rate of fall of the GFR ranged between 0.63 and 2.4 ml/min/month with a mean of 1.2 ml/min/month (Fig 8). Furthermore, a positive correlation was found between the rate of change of GFR and the reciprocal of the serum creatinine

level. When the reciprocal of the plasma beta$_2$-microglobulin concentration was used there was even a stronger correlation with GFR. They showed that the plasma beta$_2$-microglobulin concentration rises to levels above the normal as the GFR falls below 80 ml/min/1.73m^2. This is in clear contrast with the plasma creatinine concentration that is still within the normal range at a similar level of glomerular filtration (20). Although Parving et al, (21) found similar strong correlations between the reciprocal of the plasma beta$_2$-microglobulin concentration and the rate of decline of GFR, the cutoff point when the serum beta$_2$-microglobulin concentration exceeded the upper limit of normal was at a GFR <60 ml/min/1.73m^2.

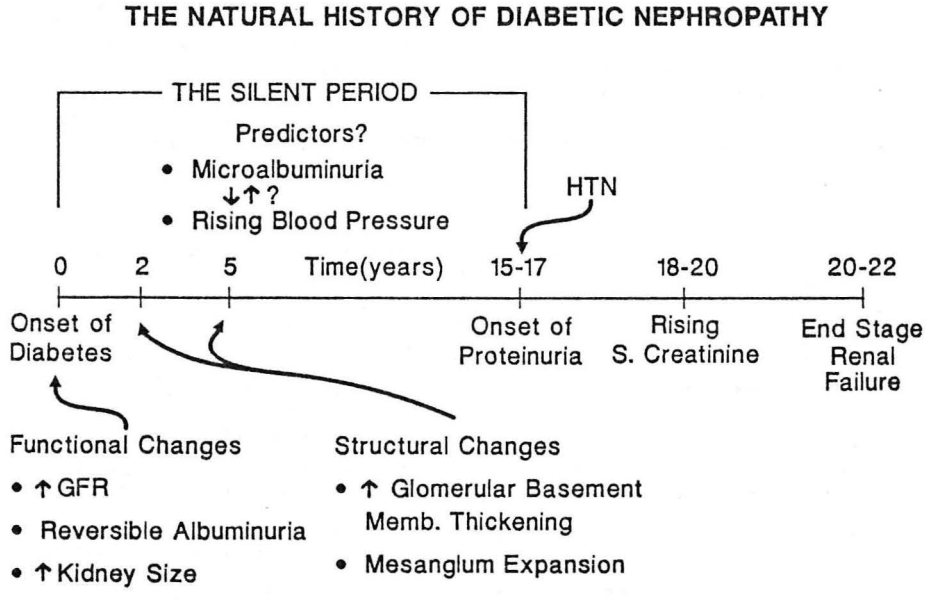
Figure 8 (Ref 19)



Important functional and structural events occur in the kidney of diabetic patients during the 1-2 decades that precede the onset of overt clinical proteinuria. There is now overwhelming evidence of a "silent period" with demonstrable pathologic glomerular changes that occur without any clinical manifestations. At some point in this "silent period" a stage of early diabetic nephropathy may develop. The only measurable clinical manifestation of this early diabetic nephropathy is an increased urinary albumin excretion rate (22). As clearly reviewed by Unger and Foster, the process leading to diabetic

nephropathy seems to start with the onset of diabetes (23). Mogensen's original classification of the different stages of diabetic renal disease clearly separated the silent period from the microalbuminuric stage. He called the period of increased urinary albumin excretion, incipient or early diabetic nephropathy (24). Figure 9 summarizes the natural history of diabetic nephropathy starting from the early structural and functional manifestations all the way up to the development of proteinuria and end stage renal failure. The role of microalbuminuria and its intricate relationship with rising blood pressure levels in the prediction of future diabetic nephropathy will be discussed below.

Figure 9



III. MICROALBUMINURIA AND EARLY DIABETIC NEPHROPATHY

1. Predictive Value:

Keen and Chlouverakis developed the first urinary albumin radioimmunoassay (RIA) and conceived the original idea for their population-based Bedford study that subclinical elevations of urinary albumin excretion in non proteinuric subjects may indicate an early stage of diabetic nephropathy (25,26).

Substantial evidence is available to suggest that a persistent elevation of urinary albumin excretion, without clinically overt proteinuria, strongly predicts a later progression of diabetic renal disease (27-32). Table 3 summarizes the long term studies that have examined the predictive value of persistent microalbuminuria. Parving et al (27), were probably the first to longitudinally attempt to identify patients at high risk of developing diabetic nephropathy. After a 6 year follow up, 5 of the 8 patients with an elevated albumin excretion rate (AER) mean 155 ± 26 mg/24h, had subsequently developed persistent overt proteinuria, elevated serum creatinine and raised blood pressure. One patient developed intermittent proteinuria. In contrast, only 2 of 15 patients with normal AER developed proteinuria.

Table 3

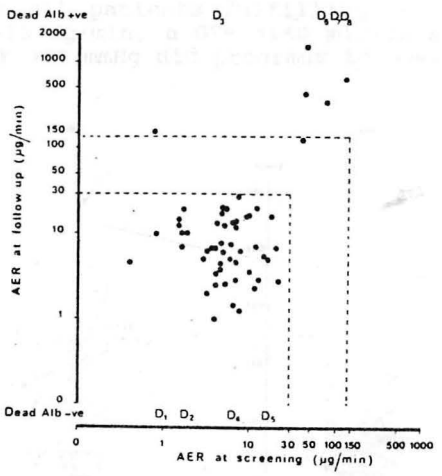
PREDICTIVE VALUE OF MICROALBUMINURIA

Study	Type of DM	No. of Patients	Follow-up (yr)	No. Pts at Follow-up	Cutoff AER µg/min	Pts. Progression
Parving et al 1982	• Age 16-40yr • Onset <31yr • Duration 10-25yr	25	6	23 (92%)	28	>28 = 6/8 (75%) <28 = 2/15 (13%)
Viberti et al 1982	• Insulin treated • Age <60yr	84	14	63 (75%)	30	>30 = 7/8 (88%) <30 = 2/55 (4%)
Mogensen and Christiansen 1984	• Onset <20yr • Duration 7-19yr	44	10	43 (98%)	15	>15 = 12/14 (86%) <15 = 0/29 (0%)
Mathiesen et al 1984	• Age <50yr • Onset <35yr	71	6	71 (100%)	70	>70 = 7/7 (100%) <70 = 3/64 (5%)

Viberti et al, (28) reported a cohort study of 63 insulin treated diabetic subjects screened in 1966-67 and reassessed 14 years later. Persistent dipstick positive proteinuria developed in 7 of the 8 patients (88%) with an overnight AER > 30 µg/min and in only 2 of the remaining 55 (4%) patients who had an AER

below that level (Fig 10). Therefore, the risk of the microalbuminuric group developing diabetic nephropathy was 24 times higher than patients without elevated AER's.

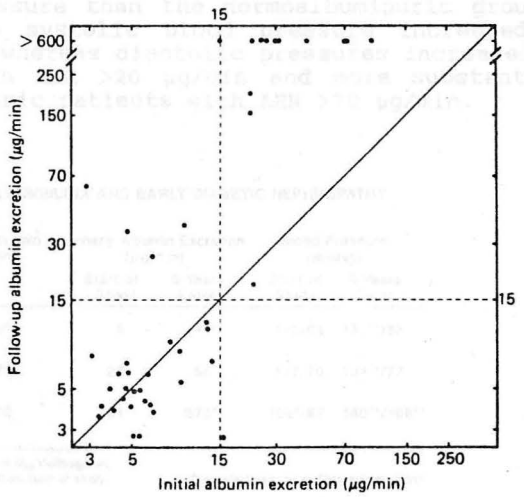
Figure 10 (Ref 28)



Albumin excretion rate (AER; log scale) at screening and at follow-up.

Recently Mogensen and Christensen (29) have shown that 80% of IDDM with AER >15 µg/min, will develop clinical nephropathy over the next 10 years. Of the 14 patients with an initial AER at or above 15 µg/min, 12 had clinically detectable proteinuria (>0.5 g/24h) or an AER >150 µg/min at the subsequent examination. Of the 29 patients who initially had an AER lower than 15 µg/min, none had subsequent clinically detectable proteinuria, although 4 later developed microalbuminuria (Fig 11).

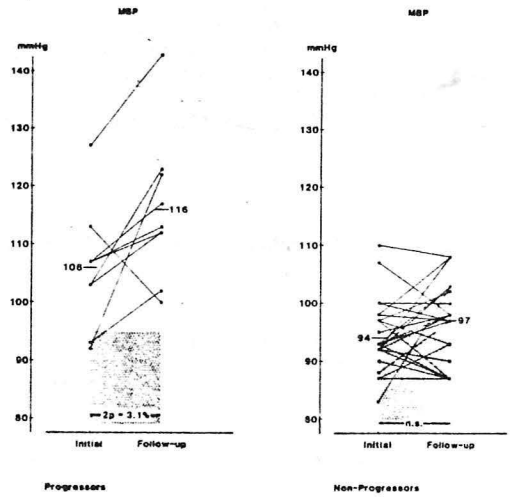
Figure 11 (Ref 29)



Follow-up albumin excretion as a function of initial albumin excretion in 43 young male diabetics followed for 7–14 yr, mean 10.4 yr ± 3 (SD).

Patients whose condition progressed to clinically overt proteinuria had elevated glomerular filtration rates and higher blood pressures at the initial examination. Furthermore, the blood pressure showed a clear rise at follow-up in the patients who progressed (Fig 12). A predictive index was suggested by the authors because all patients fulfilling the criteria of a urinary AER at or >15 µg/min, a GFR >150 ml/min and a diastolic blood pressure at or >90 mmHg did progress to overt nephropathy.

Figure 12 (Ref 51)



Mathiesen et al (30), from the Steno Memorial Hospital, reported findings similar to the above studies, but the levels of AER that predicted nephropathy were higher (>70 µg/min). At the start of the study the microalbuminuric patients had higher systolic blood pressure than the normoalbuminuric group (Table 4). At follow-up systolic blood pressure increased in all groups of patients whereas diastolic pressures increased only in those patients with AER >20 µg/min and more substantially in those microalbuminuric patients with AER >70 µg/min.

Table 4 (Ref 30)

MICROALBUMINURIA AND EARLY DIABETIC NEPHROPATHY

Urinary albumin (µg/min)	Urinary Albumin Excretion (µg/min)		Blood Pressure (mmHg)	
	Start of Study	6 Years Later	Start of Study	6 Years Later
< 20	8	14**	122/81	131**/82
21- 70	26	56	115/70	134**/77
71-200	91	570**	139*/87	160**/108**

* $p<0.05$ vs $U_{Alb}V<20$ µg/min;
** $p<0.05$ from start of study;

(From Mathiesen et al. Diabetologia 1984)

Mogensen (31) has also clearly shown that microalbuminuria predicts clinical proteinuria and increased mortality in patients with Type II diabetes mellitus. Clinical proteinuria developed in 22% of patients with microalbuminuria but in only 5% of the patients with AER <30 µg/min (Table 5). The survival rate of patients with a long duration of diabetes (>11 years) was 4.5% in the group with AER 30-140 µg/min compared with a 57% survival rate in patients with an AER <15 µg/min and same duration of disease. A substantially increased mortality risk in non insulin-dependent diabetics with an elevated AER was also found by Jarrett et al, (32) as indicated in Table 5 which also summarizes the previous Danish study in Type II diabetes. In Jarret's study of 25 survivors, 24 had AER values <10 µg/min, whereas 6 of 17 deceased had an AER >30 µg/min The mortality risk for subjects with an AER >30 µg/min was 3.3.

Table 5

PREDICTIVE VALUE OF MICROALBUMINURIA IN TYPE II DM

Study	Type of DM	No. Pts	Initial Age (yr)	Follow-up (yr)	No. Pts at Follow-up	Cutoff AER µg/min	No. Pts with Progression	Mortality
Jarret et al 1984	• Tyoe II DM • Age <60yr	42	52	14	42 (100%)	30	———	>30 = 6/7 <30 = 11/35
Mogensen 1984	• Age 50-75yr • Onset >45yr	232	67	10	232 (100%)	30	>15 = 12/14 <15 = 0/29	+148% +37%

2. Diagnosis of Microalbuminuria:

Microalbuminuria can be defined as an increased urinary albumin excretion above the upper limit of normal but not detectable by standard clinical tests. The albumin excretion rate (AER) measured by a sensitive RIA in healthy subjects varies between 2.5 to 25 mg/24h with a mean around 9.5 mg/24h (33). By use of timed urine collections, the normal values of AER can be more narrowly defined with a mean of 4.3 ± 1.3 µg/min, with a range of 2.3-8.3 µg/min (34). In normal subjects, albumin represents up to 11% of the total urinary protein excretion. In patients with increased AER the proportion of albumin rises to 22%. Diabetic patients with dipstick positive urine have a total urinary protein excretion >0.5 g/24h, of which 50% is albumin (35). The glomerular origin of the microalbuminuria found in insulin-dependent diabetic

patients is supported by the concommitant finding of a normal excretion of beta$_2$-microglobulin, a sensitive indicator of tubular reabsorptive capacity (36).

Initially there was some confusion regarding the definition of microalbuminuria because of the different, arbitrary, cut off levels of AER used in the previous studies examining the predictive value of microalbuminuria. A consensus has now been reached that defines microalbuminuria as present when the urinary albumin excretion rate (AER) is greater than 20 µg/min but less or equal to 200 µg/min (Table 6). The diagnosis of early diabetic nephropathy is made when microalbuminuria is found in 2 out of 3 urine samples collected within a 6 month period (37).

Table 6

EARLY DIABETIC NEPHROPATHY

Albumin Excretion Rates

- Normoalbuminuria (Dipstick (-)) <20 µg/min (<30 mg/24h)
- Microalbuminuria (Dipstick (-)) 20-200 µg/min (30-300 mg/24h)
- Overt Proteinuria (Dipstick (+)) >200 µg/min (>300 mg/24h)

Diagnosis

- Persistent Microalbuminuria Levels Found In At Least 2 Out of 3 Urine Samples Collected Within 6 Months

Note that multiple urine collections are required because AER can have a daily variation as high as 47% (38). The reasons for this high coefficient of variation among multiple samples remains largely unknown, but several factors such as incomplete urine collections, diet, physical activity and differences in metabolic control and blood pressure levels might influence the AER. Table 7 lists the causes of transient elevations of urinary albumin excretion that need to be considered before categorizing a patient as having microalbuminuria.

Table 7

TRANSIENT MICROALBUMINURIA

Causes

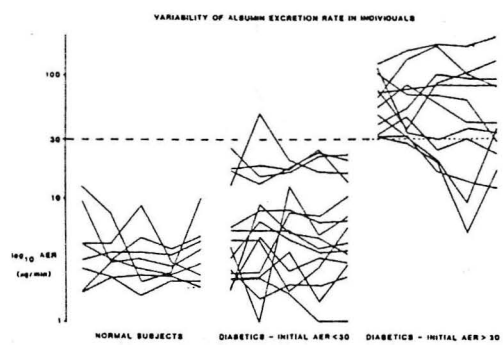
- Poor Glycemic Control
- Urinary Tract Infection
- Physical Exercise
- Essential Hypertension
- Cardiac Insufficiency
- Water Loading

In regards to transient albuminuria related to poor glycemic control, Mogensen found, at the time of diagnosis of diabetes, slight elevations of AER that promptly reverted to normal with insulin therapy (39). Even short periods of poor glycemic control would elevate the AER as shown by Parving et al, when insulin therapy was deliberately withdrawn in Type I diabetic patients (40). However, the prevalence of real and persistent microalbuminuria remains to be established.

Enthusiastic attention was initially given to exercise-induced albuminuria in an attempt to establish a provocative test that might identify an earlier stage of diabetic nephropathy (41-45). Under conventional glycemic control, diabetic patients with normal resting AER show marked albuminuric response to physical exercise compared to matched non-diabetic controls. In most studies patients with microalbuminuria responded with an even greater potentiation of AER. However, exercise-induced albuminuria may have no predictive value and adds no additional information to that obtained with timed urine collection (under basal conditions) that measure AER.

There is still some controversy regarding the issue of what urine collection method is the most practical and reliable to diagnose microalbuminuria. A variety of collection techniques have been used for the determination of AER. At Guy's Hospital in London, they used timed overnight urine collections (28) whereas the Steno group measured 24 hour urine samples (30). Mogensen in Aarhus used short-term morning samples collected hourly (31). As mentioned above, one of the difficulties interpreting AER is the wide day to day variation, that can be as high as 50%, when 24h urine collections are used (38). Even timed overnight urine collections have a 38% coefficient of variation as shown by Cohen et al (46), who studied normal subjects and normoalbuminuric and microalbuminuric diabetic patients who provided 5 timed overnight urine collection over a 6 week period (Fig 13).

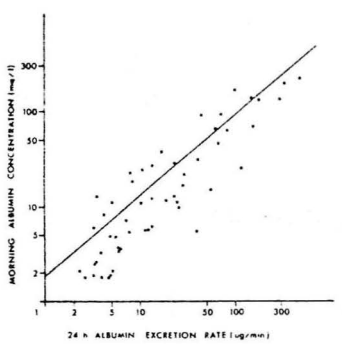
Fig 13 (Ref 46)



Albumin excretion rates (log scale) from five consecutive collections in normal subjects (left-hand panel), low risk diabetics (central panel) and high risk diabetics (right-hand panel) represented by single segmented lines

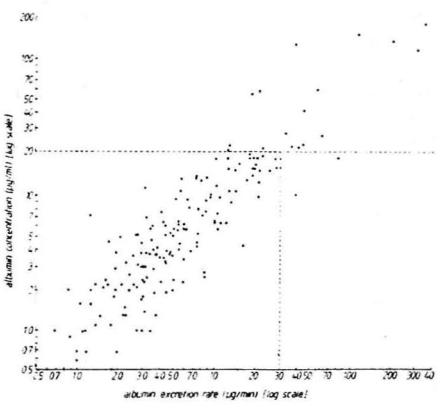
More recently Eshoj et al (47) compared overnight, morning and 24 hour urine collections in the assessment of microalbuminuria. Fifty four Type I diabetic patients were asked to perform a fractionated 24h urine collection at home, starting with the morning collection and ending with the overnight collection. AER was 25% lower in the overnight urine samples compared to the AER in the 24h and in the morning urine. Furthermore, both the overnight and morning urine samples had a sensitivity of 90% (proportion of true positives correctly identified) and a specificity of 88% (proportion of true negatives correctly identified) to predict a 24h AER within the microalbuminuric range (20-200 µg/min). The concentration of albumin in the early morning sample showed a strong correlation with the 24h AER (Fig 14). Similar results were previously reported by Gatling et al (48) who demonstrated that an albumin concentration >20 µg/ml in an early morning urine sample predicts an overnight AER >30 µg/min. In 175 patients, the sensitivity of this screening test was 86%, specificity 97%, and a predictive value 71%. If an albumin/creatinine ratio is used for the morning sample, the sensitivity improves from 86% to 100% without significantly lowering the predictive value of the screening test. A strong correlation between early morning albumin concentration was found in this study with the overnight AER (Fig 15).

Figure 14 (Ref 47)



The albumin excretion rate in 24 h urine versus the concentration of albumin in morning urine. Linear regression analysis

Figure 15 (Ref 48)



Graph showing the correlation between albumin concentration in overnight urine specimens and albumin excretory rates in 175 diabetics

To sum up, it appears that early morning albumin determinations provide a simple practical and reliable strategy

to screen for microalbuminuria. If an elevated albumin concentration is detected, the diagnosis of microalbuminuria needs to be confirmed with a series of timed overnight urine collections, which are more convenient to the patient than the 24h collections.

3. The Natural Course of Microalbuminuria:

The natural history of persistent micoalbuminuria remains unknown. The studies discussed above proposing a predictive value for microalbuminuria have the limitations that they were not originally planned prospectively nor were they conducted longitudinally (27-32). All were done retrospectively and their results are based on measurements of urinary albumin excretion rates performed sometime in the past, in selective groups of Type I diabetic patients, and re-examined again several years later.

Several cross-sectional studies have examined the possible role of blood pressure and renal hemodynamics as identifiable factors in the course of early diabetic nephropathy. Most of these studies indicate a strong association between rising blood pressure levels and microalbuminuria as a manifestation of renal involvement in Type I diabetes (30, 49-51). Mathiesen et al, (30) showed that 67 of 227 IDDM subjects (30%) had an elevated AER (>20 µg/min). The systolic and diastolic blood pressures were significantly higher in the microalbuminuric patients (Table 8). HbA_1C was slightly higher in the microalbuminuric patients but showed no correlation with the AER. GFR was higher than normal in those patients with early nephropathy though not different from that of those with normoalbuminuria. The AER was independent of duration of the diabetes.

Table 8 (Ref 30)

THE STENO CROSS-SECTIONAL STUDY

Urinary Albumin (μg/min)	HbA_{1c} (%)	Systolic BP (mmHg)	Diastolic BP (mmHg)	GFR (ml/min)
< 20	8.9	124±14	79±8	122±18
21- 70	9.3	123±12	79±10	126±22
71-200	9.7	131±11*	85±7*	125±26

* = $p<0.05$ vs <20 μg/min (From Mathiesen et al, Diabetologia, 1984)

As clearly seen in Table 9, diabetic subjects with microalbuminuria tend to have significantly higher blood pressure levels compared to matched normoalbuminuric patients (49). However, these rising blood pressure levels, although elevated, are below the conventionally accepted hypertensive level.

Table 9 (Ref 49)

RENAL FUNCTION AND BLOOD PRESSURE IN DIABETIC NEPHROPATHY

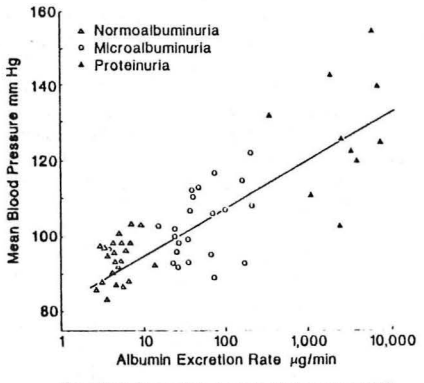
	Controls (n=18)	Normoalbuminuria (n = 23)	Microalbuminuria (n = 23)	Proteinuria (n =10)
Age (yr)	28.6	27.6	26.9	31.0
Duration (yr)	-	15.7	15.3	20.0
Albumin excretion (μg/min)	4.3	4.8	48.8	2705
Blood Pressure (mm/Hg)	115/73	122/80	133/88	167/109
Glomerular filtration rate (ml/min)	123	132	142	89

(From Mogensen and Christensen, Hypertension, 1985)

Furthermore, Figure 16 shows a strong positive correlation that can be found when mean arterial blood pressure levels from normoalbuminuric, microalbuminuric and proteinuric patients are plotted against urinary albumin excretion rates (51). It seems as if developing hypertension is in fact a continuum process that starts long before, and not as originally thought, at the onset of proteinuria.

Figure 16 (Ref 51)

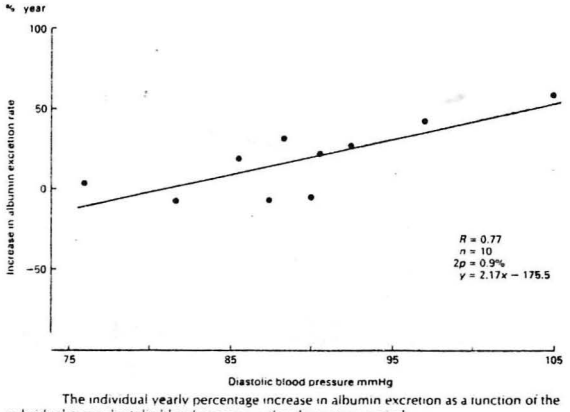
MICROALBUMINURIA AND BLOOD PRESSURE



(From Mogensen and Christensen, Hypertension, 1985)

In the only longitudinal study available, Christensen and Mogensen (49) followed 10 microalbuminuric patients in an uncontrolled longitudinal fashion for 5 years. These patients showed an average AER increase of 20%/year. Of note is that the increase in AER correlated significantly with the increase in diastolic blood pressure (Fig 17).

Figure 17 (Ref 49)



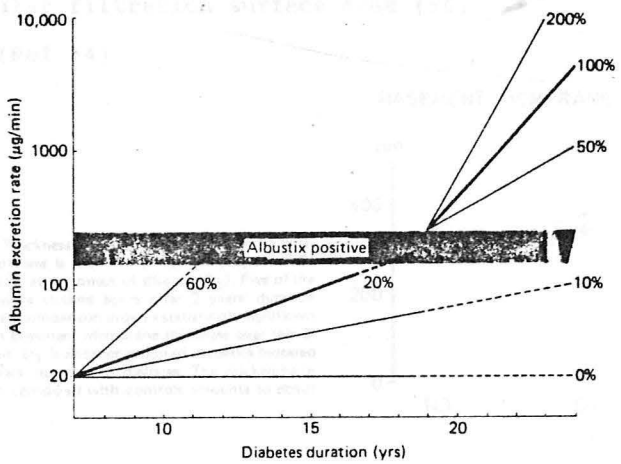
The individual yearly percentage increase in albumin excretion as a function of the individual mean diastolic blood pressure in the observation period

Renal structural-functional abnormalities is the traditional and most acceptable view to explain the rising blood pressure levels seen in diabetic nephropathy. However, of great interest are the recent reports proposing an explanation for the frequency of hypertension and diabetic nephropathy occuring in only one third of all patients with insulin-dependent diabetes. The susceptibility to develop diabetic nephropathy may be determined by a genetic predisposition to hypertension in this subset of patients (52,53). Krolewski et al, (52), studied possible markers for the genetic predisposition to hypertension by comparing the frequency of a history of parental hypertension and the maximal velocities for sodium transport systems in red blood cells. They found that in 33 patients with diabetic nephropathy the maximal velocity of lithium-sodium countertransport in red cells was significantly higher than in 56 diabetic control patients without nephropathy. Also in those patients with diabetic nephropathy a higher percentage of their parents had clinical hypertension than did the parents of patients without diabetic nephropathy. The excess risk associated with both these indicators of a predisposition to hypertension was evident mainly in patients with poor glycemic control during the first decade of diabetes. Mangili et al (53), confirmed these findings by demonstrating higher rates of sodium-lithium contertransport in patients with diabetic nephropathy when compared with diabetic patients without renal disease and with non-diabetic patients with other types of renal

diseases. These hypothesis remain speculative and require further confirmation.

As stated above, the natural history of early diabetic nephropathy remains unknown. Only long term carefully designed prospective studies may give some answers. In the meantime, hypothetical models like the one shown in Figure 18 may be considered acceptable.

Figure 18 (Ref 22)



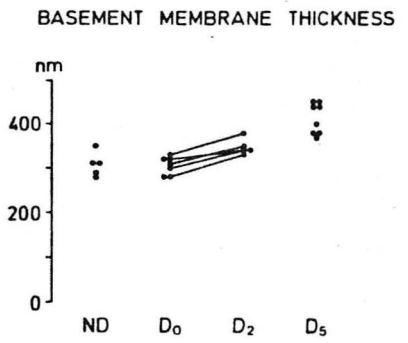
4. Pathogenesis of Microalbuminuria:

Much controversy exists regarding the mechanisms that affect the glomerular filtration barrier in microalbuminuric patients with early diabetic nephropathy. The transglomerular passage of plasma proteins depends on several factors, including 1) structural changes in the glomerular membrane, 2) renal hemodynamics such as renal plasma flow and the transcapillary hydraulic pressure, and 3) filtration surface area abnormalities at the pore-size or pore-charge level. Mechanisms that explain the increased albumin clearance across the glomerular filter can therefore be found at different sites.

4a. Glomerular Structural Changes

Sophisticated morphometric studies performed on kidney biopsies by Osterby's group in Aarhus, showed that GBM and mesangial basement membrane-like material are normal at diagnosis of Type I diabetes (54). However, within 1.5-2.5 years the GBM width increases 10-15%. After 5 years of diabetes, the GBM width is 30% greater than it is in controls (Fig 19). The same investigators by use of stereological electron-microscopic methods of renal biopsies from short term IDDM patients have demonstrated an increase in glomerular size (55) and glomerular filtration surface area (56).

Figure 19 (Ref 54)



Thickness of the peripheral glomerular basement membrane is identical in control subjects (ND) and diabetics at the onset of disease (D_0). Five of the diabetics were studied again after 2 years' duration (D_2). Paired comparison shows a statistically significant increase in basement membrane thickness over this 2-year period. D_5 is another group of diabetics biopsied after 5 years' duration of diabetes. The thickening in this group compared with controls amounts to about 30%.

GBM thickening and expansion of the glomerular mesangium, primarily due to the enlargement of the mesangial matrix, is a constant finding in most patients with diabetes. It seems that initially the pattern is of a progressive GBM thickening, and then most of the basement membrane-like material eventually accumulates in the mesangial region.

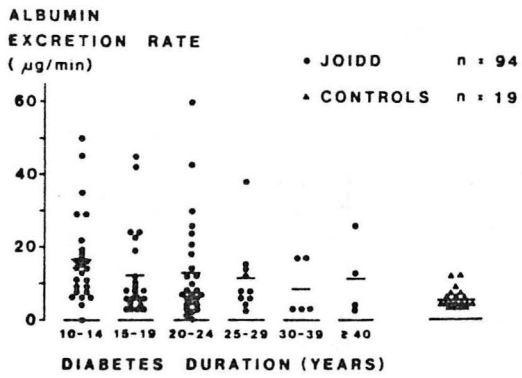
The implications of all the observed early, structural, renal changes on the development of diabetic kidney disease remains to be established. Diabetic nephropathy should be regarded as a continuum that evolves from early renal hypertrophy through the late changes of advanced structural distortion of glomeruli, renal vasculature, and interstitium. The end result of the basement membrane and mesangium accumulation is glomerular occlusion. This event occurs around 15 years of diabetes, and it may be related to mesangial expansion encroaching on the subendothelial space, eventually compromising the glomerular capillary lumen and blood flow (57). The number of occluded glomeruli appears to increase as the

duration of diabetes increases. In autopsy studies of patients with long-standing IDDM, Gunderson and Osterby (58) found a relationship between the number of glomeruli with capillary occlusions and both, duration of the disease and degree of renal failure.

However, an intriguing dissociation occurs when structural and morphological changes in the kidney are related to renal function in IDDM patients. Whereas 30-35% of all IDDM patients will develop overt clinical diabetic nephropathy, nearly 70% of patients will never develop clinical renal disease, despite histological evidence of glomerulosclerosis in nearly all IDDM patients after several years of the disease.

To elucidate the relationship between clinical diabetic renal disease and renal pathology, the Steno group studied autopsy material from 34 long-term IDDM patients. Half of these patients had no clinical evidence of nephropathy, and the other 17 matched patients had severe clinical nephropathy (59,60). Patients who had clinical renal disease had significantly more interstitial tissue and glomerular mesangium expansion and less open glomerular capillaries that the diabetic subjects without clinical nephropathy. However, severe glomerulosclerosis was also seen in patients without clinical evidence of nephropathy. Remarkable mesangial expansion was seen in most of the patients with clinical renal disease, but it was also present in several diabetic subjects who did not have clinical nephropathy (Fig 20). The area of open capillaries appeared to be a good light-microscopic indicator of clinical nephropathy.

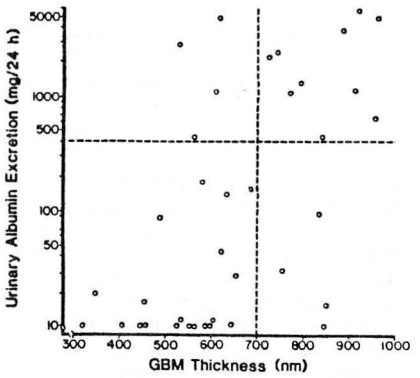
Figure 20 (Ref 59)



Mauer et al, (61), have reported elegant studies of renal biopsies from 45 patients with IDDM. These specimens were examined by semiquantitative light microscopic and quantitative

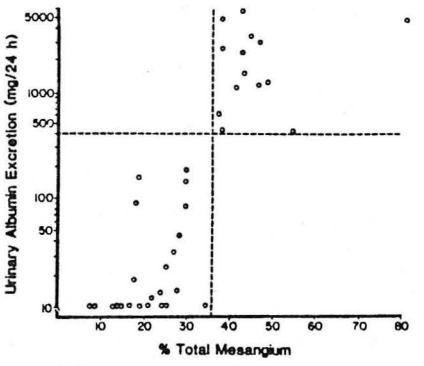
electron microscopic stereologic morphometry. These patients had IDDM for 2.5 - 29 years, but only 16 patients had clinical evidence of nephropathy. The renal biopsies were performed as part of their evaluation as potential pancreas transplant recipients. The total mesangium volume had a strong inverse correlation with the capillary filtration surface area. There was no significant relationship between creatinine clearance and GBM thickness. The mesangial expansion had a strong inverse correlation with creatinine clearance, however. The gradual progression of GBM thickening with time can not explain the alterations in glomerular permselectivity manifested by increased albumin excretion. A gradual increase in albuminuria would be expected as GBM thickening increases; however, this study indicated that marked GBM thickening is compatible with intact permselectivity, and minimal GBM thickening can be associated with massive proteinuria (Fig 21). Note, however, that this study was not designed to evaluate patients with microalbuminuria and early diabetic nephropathy. Microalbuminuria levels were found in 6 of 24 patients without overt diabetic nephropathy, but the assay of urinary albumin used had a low sensitivity, and the number of urine collections was not specified. No structural glomerular parameter precisely predicted AER. However, all patients whose kidneys showed a total mesangial volume >37% had >400 mg/24h AER (overt proteinuria) and hypertension (Fig 22). An AER between 40 and 400 mg/24h was not necessarily associated with more advanced glomerular changes. Conversely, patients with severe glomerulopathy, regularly seen in patients with clinical nephropathy, had normal AER. This meticulous study demonstrates that clinical diabetic nephropathy does not become manifest until anatomical renal lesions become far advanced.

Figure 21 (Ref 61)



UAE and GBM thickness. The interrupted lines represent the graphic limits of the chi-square, which was calculated to be 5.98, NS.

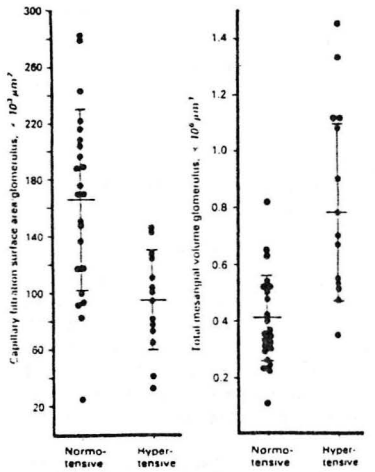
Figure 22 (Ref 61)



UAE and percentage total mesangium. The interrupted lines represent the graphic limits of the chi-square, which was calculated to be 27, $P < 0.0005$. In this and next figure note the triple log scale for UAE; in both figures points near the abscissa (at 10 mg/24 h) represent UAE rates below the sensitivity range of the urinary albumin test.

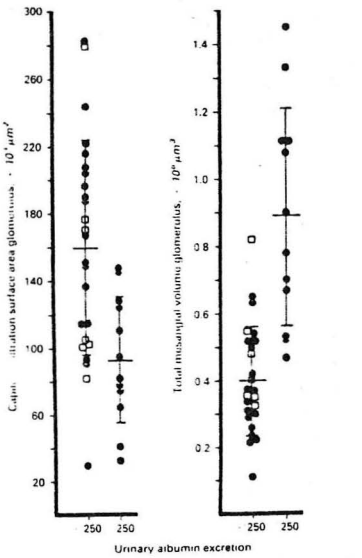
Recently Mauer and co-workers (62) extended their observations on glomerular and mesangial volume to specifically assess capillary filtration surface in 37 Type I diabetic patients with a broad spectrum of renal function after 5 to 33 years of diabetes. Glomerular filtration surface was greater and mesangial volume smaller in normotensive than hypertensive subjects (Fig 23). Patients with urinary albumin excretion >250 mg/24h (proteinuric range) had restricted filtration surface and expanded mesangial volume as compared with patients with urinary albumin <250 mg/24h (Fig 24). Of note is that no structural differences were noted between the microalbuminuric and normoalbuminuric patients (Fig 24).

Figure 23 (Ref 62)



Capillary filtration surface area/glomerulus and mesangial volume/glomerulus in normotensive and hypertensive patients.

Figure 24 (Ref 62)



Capillary filtration surface/glomerulus and mesangial volume/glomerulus in patients with urinary albumin excretion <250 mg/24 hr and >250 mg/24 hr. □, patients with microalbuminura.

The enigma on the structural substrate in microalbuminuria could not be clarified by a recent report on 35 Type I normotensive diabetic patients with normal creatinine clearances (63). Morphometric analysis of renal biopsies comparing normoalbuminuric (n=23) and microalbuminuric patients (n=12) revealed no differences in mean glomerular volume, average mesangial volume per glomerulus, average surface area and GBM thickness. None of these structural parameters correlated with AER. It was concluded that microalbuminuria was not associated with more severe glomerular pathology nor did normoalbuminuria

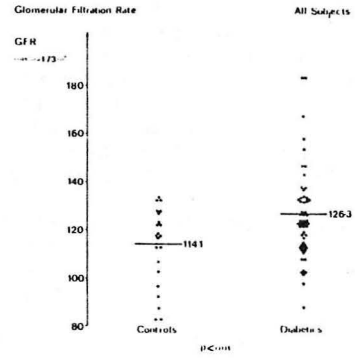
excluded the presence of significant glomerular lesions. This is in contrast with a previous report from Osterby et al (64), who found that patients with early diabetic nephropathy, defined as a AER between 20 and 600 µg/ml and a GFR >100 ml/min, appeared to have more advanced renal structural changes than patients without this condition. They also had less glomerular destruction than patients with advanced diabetic nephropathy.

In summary, it appears that morphological changes themselves cannot be the chief cause of the increased AER seen in early diabetic nephropathy. Kidney biopsy is not a routine procedure to be used in patients with diabetic nephropathy. However, longitudinal structure-function studies can be considered as a research tool to ascertain prospectively the course of the diabetic kidney disease and to assess the impact of different therapeutic modalities. The rationale from the Minnesota group is as follows: "There is no other progressive, primarily glomerular disorder with such a high risk of renal failure in which there is such a reluctance to perform renal biopsies as in patients with IDDM. If the onset of clinical nephropathy represents the beginning of the end of useful function of the kidneys, it may only make sense to perform renal biopsies before renal disease is clinically detectable" (65).

4b. Glomerular Hyperfiltration

Elevated GFR in IDDM patients at different stages of their disease have been reported in several studies (66-69). GFR is increased by 40% in newly diagnosed patients and by 25% in young short term IDDM patients with <15 years of the disease (68). This increase in GFR, characteristic of perhaps 25-30% of all IDDM (Fig 25) patients, persists for many years (69). In patients who apparently escape overt clinical nephropathy, it is probably unremitting (70).

Figure 25 (Ref 69)



14 Diabetics have GFR≥135 (25·4%)

Glomerular filtration rate (GFR) measured in 22 normal subjects and 55 clinically non-proteinuric, insulin-dependent diabetic subjects, matched for age. Fourteen diabetics (25%) have clearly supranormal GFR

The mechanisms for this hyperfiltration are not entirely clear. The elevated GFR associated with poor metabolic control can be reduced substantially with effective insulin treatment, as initially shown by Mogensen et al (71). Furthermore, even 3 days of insulin treatment will reduce the GFR from 160 ± 9 to 141 ± 6 ml/min/1.73m² in newly diagnosed IDDM. After 8 days of treatment, a 17% reduction in GFR is seen (72). It appears that GFR is somehow related to the degree of glycemic control(73). Studies performed in normal subjects and short term IDDM patients have revealed that oral glucose loading does not cause an increase in GFR (74), whereas intravenous glucose administration induces a significant 5% elevation in GFR (75).

Insulin per se does not seem to induce alteration in GFR, as shown by studies that use insulin and glucose infusions that maintain the blood glucose levels constant (76,77). Glucagon infusions administered to normal subjects and IDDM patients in doses low enough to achieve plasma concentrations similar to those observed in poorly controlled diabetes, have been shown to induce significant elevations in GFR (78,79). The magnitude of the increase in GFR was 6% and probably was not due to glycemic changes. Glucagon, however, may be only one of several factors affecting glomerular hemodynamics because well controlled IDDM patients with normoglucagonemia still have high GFR's (79). The influence of human growth hormone (HGH) has also been studied as uncontrolled diabetes is associated with high HGH levels (80), and acromegalic patients also have an elevated GFR (81). Daily subcutaneous administration of 6 IU of HGH for a week increased the GFR by 9% in normal subjects (82) and by 7% in IDDM patients (83).

The acute changes seen in GFR after increments in plasma concentrations of glucose, glucagon, and HGH to levels similar to those seen in IDDM were 5%, 6%, and 7%, respectively. Unless an additive effect is postulated, these changes cannot fully explain the hyperfiltration state seen in IDDM (84).

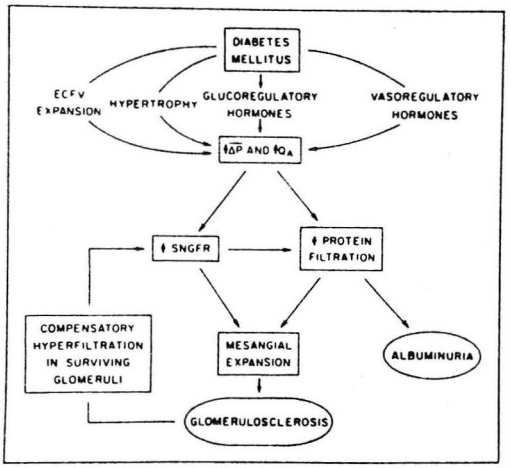
The main mechanism involved in the high GFR in IDDM may be related to the structural changes seen very early in the course of the disease (85). Increased kidney size and GFR are positively correlated and the glomerular volume and glomerular capillary surface show marked enlargements very early (55,56). Opponents (84) of the above morphological hypothesis argue that the rapid fall in GFR obtained with insulin therapy (72) cannot be explained by changes in the enlarged glomerular size and filtration surface area, because these abnormalities remain unchanged after >1 month of insulin treatment (56).

Experimental evidence suggests that hemodynamic factors play a major role and can influence the rate of progression of the diabetic nephropathy lesions (86). Unilateral nephrectomy in streptozocin induced diabetic rats clearly accelerates the progression of mesangial expansion, with lesions developing more rapidly and severely than in intact diabetic animals (87).

Similar findings are obtained with uninephrectomy in the diabetic dog model (88). By use of the classic two-kidney Goldblatt model, both streptozotocin diabetic rats and normal animals became hypertensive (89). The unclipped kidneys that were exposed to the elevated systemic arterial pressure showed more severe glomerular lesions that kidneys from normotensive diabetic rats. Moreover, the clipped kidneys (i.e., kidneys protected from the hypertension) in the diabetic rats tended to show a lesser degree of glomerulopathy than the normotensive rats. In one of the most widely quoted case reports in medical literature, Berkman and Rifkin (90) described autopsy findings in a patient with long standing diabetes and unilateral renal artery stenosis. Classic diabetic lesions were confined to the kidney on the side of the normal renal artery. The contralateral kidney that was protected by the stenotic renal artery showed only mild ischemic changes and no pathological changes of diabetes.

These observations and the experimental evidence generated from the "remnant kidney" and "high protein" models have lead Brenner and co-workers (86,91-93) to propose that the renal hemodynamic alterations manifested as glomerular hyperfiltration initiate and determine the progress of diabetic nephropathy (Fig 26).

Figure 26 (Ref 93)

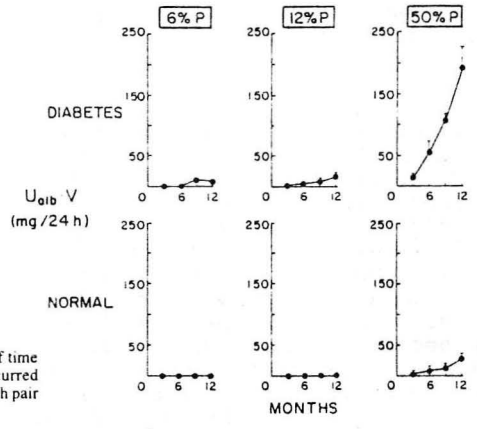


Hypothetical model of glomerular hyperfiltration in initiation and progression of diabetic nephropathy.[93]

The "remnant kidney" model, which can only be reproduced in rats, is produced by surgical ablation and infarction of approximately 90% of the renal mass of Munich-Wistar rats (91). Compensatory hemodynamic mechanisms to the reduced number of nephrons result in the establishment of hyperfiltration and hyperperfusion in the remnant kidney that leads to pathologic changes similar to those seen in diabetic nephropathy. An increase in the single nephron glomerular flow and

transcapillary hydraulic pressure in the nephrons of the remaining kidney may cause changes in the permselective properties of the glomeruli. This then results in albuminuria (92). More recently Zatz et al (94), extended these observations using a "high protein" model. They attempted to dissociate the effects of glomerular hyperperfusion from chronic hyperglycemia. In order to manipulate glomerular hemodynamics, 3 groups of streptozotocin diabetic rats with similar hyperglycemic control and 3 groups of normal rats were given diets containing 6%, 12% and 50% protein. Diabetic rats on 50% protein diet (D50) had higher single nephron glomerular filtration rate and higher mean glomerular transcapillary hydraulic pressure than in all other groups. This D50 had marked and progressive albuminuria (Fig 27) and histologically had areas of sclerosis in nearly 20% of glomeruli in contrast to <2.5% frequency of such lesions in the rest of the groups. Brenner's and co-workers concluded that moderate hyperglycemia in rats does not lead to glomerulopathy as long as glomerular hyperperfusion is prevented. An objection to this study is that histologic examination was very rudimentary, and no morphometric analysis of glomerular structures was performed in all groups. Furthermore, if indeed glomerular hyperperfusion is so relevant, then normal rats on 50% protein diet should have been more affected.

Figure 27 (Ref 94)



Urinary albumin excretion (U_{alb}·V) as a function of time in long-term studies. Marked and progressive albuminuria occurred only in the D50 group. Percent protein in diet is given above each pair of graphs for matched diabetic and control groups.

A reasonable suggestion that may reconcile the role of glomerular hemodynamic with the glomerular structural changes is that hyperperfusion becomes critical when the capillary luminal space and the peripheral capillary filtering surface of the glomeruli are diminished as a consequence of marked mesangial expansion (95). This hypothesis implies that glomerular hyperfiltration develops in patients with established glomerular lesions and that the compensatory hemodynamic changes will

accelerate the progress of diabetic nephropathy. However, as discussed above it is puzzling that almost all IDDM patients have increased GBM thickness with mesangial expansion (60,61) after several years of disease, but still only 30-35% go on to develop clinical diabetic nephropathy (10,12). In addition, elevated GFR does not occur in all IDDM and can be unremitting after long diabetes duration. Furthermore, the removal of a single kidney in normal rats produce hemodynamic changes identical to those seen in experimental diabetes in the intact rat. Yet, despite those similar hemodynamic changes, these non-diabetic animals fail to develop lesions similar to diabetic nephropathy even after prolonged observation (87).

In summary, it appears that in the absence of diabetes, clinically important glomerulopathy does not develop. Compensatory hemodynamic changes might contribute substantially to the progression of diabetic nephropathy, but sufficient evidence is not available to implicate this as the primary initiating pathogenic mechanism.

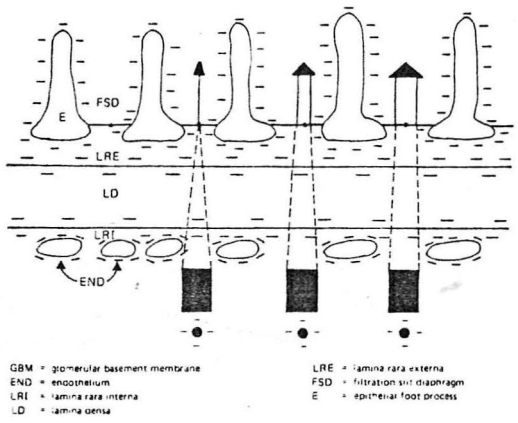
4c. Abnormalties in Glomerular Filtration Barrier

It has been postulated that the primary event responsible for albuminuria is a qualitative change affecting the permselective properties of the glomerular barrier and that this change is independent of basement membrane thickening, mesangial expansion, and glomerular hyperfiltration (96).

The glomerular capillary filter can be regarded functionally as a membrane with pores of an average size of 55 Å that is uniformly coated by negative electrical charges (97-99). The glomerular barrier has properties of size selectivity and charge selectivity in relation to the transcapillary passage of plasma proteins (98). The pore-size selectivity of the glomerular barrier appears to be intact in diabetic patients with microalbuminuria as shown by studies that use the clearance of uncharged neutral dextran of several molecular weights (100). Normal dextran clearances are also found in experimental diabetes of rats (101). Patients with advanced diabetic nephropathy and marked proteinuria have clear evidence of increased glomerular porosity size, however (102).

The glomerular charge-selective property is conferred by fixed negative charges on the basement membrane that generate electrostatic interactions with the plasma proteins (98). Negatively charged proteins like albumin are filtered in smaller amounts than neutral molecules of a comparable size, whereas filtration of positively charged molecules is facilitated as shown in Figure 28 (103).

Figure 28 (Ref 103)



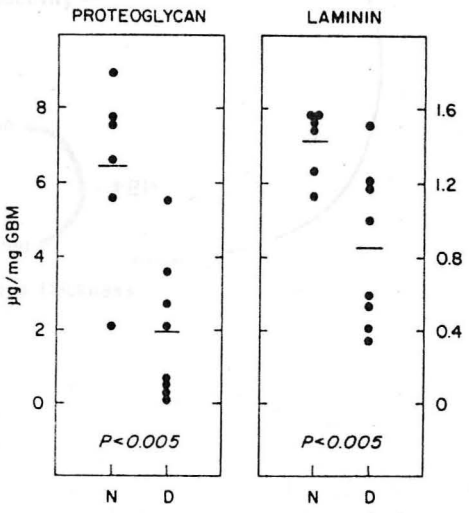
The anionic net charge of the glomerular barrier is primarily determined by glycosaminoglycans rich in heparan sulfate (104,105). The congenital nephrotic syndrome may result from failure to develop the sulfate-rich anionic sites in the lamina rara externa of the GBM as shown by quantitative cytochemical methods from kidney biopsies examined by electron microscopy (106). Removal of the heparan sulfate and other glycosaminoglycans by perfusion of rat kidneys with heparinase, greatly increases the passage of the native anionic ferritin across the GBM (107). Similar results are found in the heparinase-perfused kidney by use of 125 I-labeled albumin as a marker (108). Neutralization of heparan sulfate by infusion of the polycation protamine sulfate clearly increases AER (109). Both systemic and unilateral kidney perfusions in rats with protamine sulfate reduce the glomerular staining for polyanions and markedly increase albumin excretion. Similar results are found with polyethyleneimine as the polycation and with native or cationic ferritins as glomerular permeability markers (110).

Experimental evidence strongly suggests that the diabetic state influences the synthesis of glycosaminoglycans rich in heparan sulfate (111-113). A decreased de novo synthesis of sulfate proteoglycans was demonstrated by a 30-40% less in vitro (^{35}S) sulfate incorporation into glomerular extracellular matrices of diabetic rats compared with normal rats (112). In vivo studies with the injection of (^{35}S) sulfate into normal and streptozocin diabetic rats showed a diminished sulfation and/or production but a normal turnover of glycosaminoglycans in the GBM in experimental diabetes (113).

In early diabetic nephropathy with AERs >30 µg/min, the clearance of albumin is greater than the IgG clearance (114). Because albumin is highly anionic (pI 4.8, stokes radius 36 Å)

and IgG is a larger but essentially neutral molecule (pI 7.6, stokes radius 55 Å), these findings suggest a defect in the charge-selectivity properties of the glomerular filter in patients with microalbuminuria. Sialic acid appears to contribute <5% of the total anionic content in GBM (115). Nevertheless decreased concentrations of sialic acid in GBM have been found in diabetic patients (116). More importantly, the glycosaminoglycan component of GBMs from human diabetic kidneys has been found to be significantly decreased compared with non-diabetic control subjects (117). This observation has recently been confirmed using precise quantitation by immunochemical procedures that indicate that human diabetic glomerular basement membrane contained significantly lower amounts of heparan sulfate proteoglycan (by 30%) and laminin (by 60%) as compared with that from non-diabetic individuals (118) (Fig 29).

Figure 29 (Ref 118)



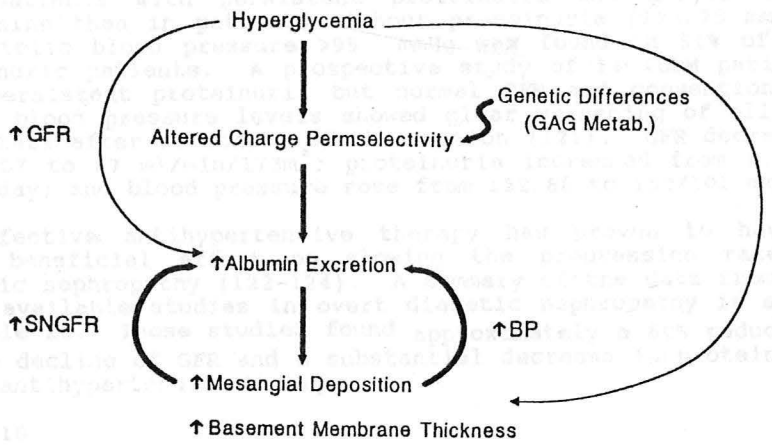
Content of heparan sulfate proteoglycan and laminin in guanidine HCl extracts of GBM from individual nondiabetic (N) and diabetic (D) human subjects. Analyses were carried out on 4 M guanidine HCl–solubilized fraction by solid-phase radioimmunoassays as described in text; values are expressed per mg dry weight of unfractionated GBM. Mean is indicated for each group, and *P* value between nondiabetics and diabetics is shown.

Therefore, the hypothesis proposed by Deckert and colleagues (96) to explain the onset and progression of early diabetic nephropathy seems very attractive. Increased albumin excretion is probably associated with a depletion of heparan-sulfate concentrations. This depletion of heparan sulfate compromises the anionic barrier to albumin. The quality of glycemic control as well as genetic differences might influence the rate of synthesis and turnover of glomerular sulfated proteoglycans. This may explain differences commonly found in prevalence and severity of diabetic nephropathy. Mesangial expansion with accumulation of albumin and macromolecules is probably due to both, an impaired capacity to clear macromolecules (119) and a

stimulated mesangium matrix production. These changes will eventually restrict glomerular capillary filtration and other glomerular hemodynamics.

Figure 30 summarizes the potential pathogenic mechanism that may result in microalbuminuria.

Figure 30



IV. THERAPEUTIC INTERVENTIONS ON MICROALBUMINURIA

If microalbuminuria is indeed a predictor for the development of late diabetic renal disease, then various therapeutic interventions can be evaluated at an early stage of the kidney disease, in an attempt to interfere with the natural course of the disease.

1. Early Antihypertensive Treatment:

Experimental and clinical evidence, as discussed above, strongly suggests that arterial hypertension accelerates the glomerular lesions of diabetic nephropathy (87-90). Moreover, mesangial expansion to an extent >37% of the glomerular volume is strongly predictive of hypertension (61).

Increased arterial blood pressure is an early feature of overt diabetic nephropathy, as shown by Parving et al (120). They found a higher mean blood pressure level (146/96 mmHg) in IDDM patients with persistent proteinuria and normal serum creatinine than in patients without proteinuria (123/75 mmHg). A diastolic blood pressure >95 mmHg was found in 51% of the proteinuric patients. A prospective study of 14 IDDM patients with persistent proteinuria but normal GFR and conventionally normal blood pressure levels showed clear worsening of all the parameters after 26 months of observation (121). GFR decreased from 107 to 87 ml/min/173m^2; proteinuria increased from 1.8 to 3.3 g/day; and blood pressure rose from 132/88 to 153/101 mmHg.

Effective antihypertensive therapy has proven to have a clear beneficial effect on slowing the progression rate of diabetic nephropathy (122-124). A summary of the data from the three available studies in overt diabetic nephropathy is shown in Table 10. These studies found approximately a 60% reduction in the decline of GFR and a substantial decrease in proteinuria after antihypertensive therapy.

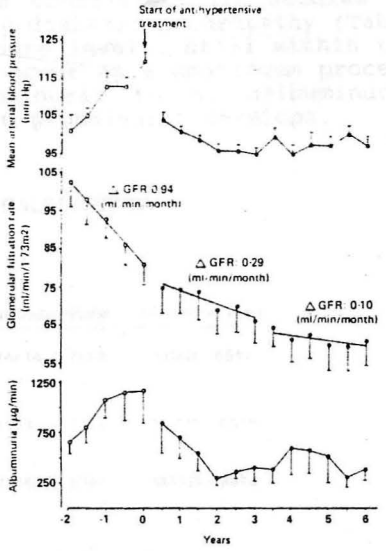
Table 10

RENAL FUNCTION DECLINE IN DIABETIC NEPHROPATHY
Effect of Antihypertensive Therapy

Study		#Pts	Age (yr)	Duration DM (yr)	Observation (mo)	GFR Pre-Rx (ml/min)	BP (mmHg)	Decrease in GFR (ml/min/mo)
Mogensen 1982	Pre-Rx	6	30	18	28	86	162/103 (123)	1.23
	On Rx				73		144/95 (111)	0.49
Parving et al 1983	Pre-Rx	10	29	16	29	80	144/99 (113)	0.91
	On Rx				39		128/84 (99)	0.39
Bjorck et al 1986	Pre-Rx	14	34	22	32		163/97 (119)	0.86
	On Rx				24		155/94 (114)	0.46

Recently Parving et al (125) confirmed and extended their previous observations by demonstrating that the beneficial effect of antihypertensive treatment on the course of diabetic nephropathy was maintained over a 72 month follow up period. The average blood pressure fell from 143/96 mmHg to 129/89 mmHg and albuminuria decreased from 1038 µg/min to 504 µg/min. The rate of decline in the GFR decreased from 0.89 ml/min/month before treatment to 0.22 ml/min/month during treatment (Fig 31). A prognostic estimate from the slope of the decline in the GFR indicates that the median period from the start of antihypertensive therapy to ESRD (GFR <5 cc/min/1.73m²) could be predicted to be extended from 7 years without treatment to 21 years with treatment.

Figure 31 (Ref 125)



—Average course of mean arterial blood pressure, glomerular filtration rate, and albuminuria before (○) and during (●) long term effective antihypertensive treatment of nine insulin dependent diabetic patients who had nephropathy.

Considerable attention has been given to the role of angiotensin converting enzyme inhibitors in the management of hypertension in diabetic nephropathy. Bjorck et al (124), found that in hypertensive patients with diabetic nephropathy, adding captopril to conventional antihypertensive therapy resulted in a mean blood pressure fall of only 5 mmHg, but the deterioration in GFR, substantially decreased from 10.3 to 2.4 ml/min/year over a 2 year period. Hommel et al, studied the effects of 12 weeks single therapy with captopril in 16 hypertensive proteinuric Type I diabetic patients (126). Arterial blood pressure fell from 147/94 to 135/86 mmHg, albuminuria fell from 1589 to 1075 µg/min and GFR from 99 to 93 ml/min/1.73m². The suggestion was made that ACE inhibitors may reduce albuminuria probably by lowering glomerular hypertension. These agents reduce efferent arteriolar resistance which is specifically increased by the vasoconstrictive action of angiotension II (127).

Support for the role of ACE inhibitors comes from the experimental evidence in rats subject to 5/6 renal ablation treated with enalapril vs "standard triple antihypertensive therapy" (128). Despite similar systemic blood pressure lowering effect, only enalapril significantly reduced the mean glomerular transcapillary hydraulic pressure resulting in greater protection against development of proteinuria and glomerular lesions. Similar protection have been shown by Zatz et al (129) using streptozotocin diabetic rats treated with enalapril.

Slightly but significantly elevated blood pressure levels have consistently been reported in cross-sectional studies in microalbuminuric patients with early diabetic nephropathy (Table 11) (30,50,51). Rising blood pressure levels, still within the conventional normal range, seem to occur as a continuum process in the transition from normoalbuminuria to microalbuminuria until finally overt hypertension and proteinuria develops.

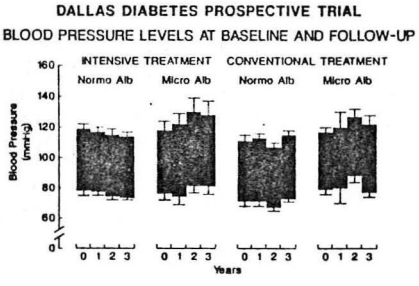
Table 11

BLOOD PRESSURE LEVEL AND MICROALBUMINURIA
Cross-Sectional Studies

Study	No. Patients	Cutoff Normal AER µg/min	Normoalbuminuria	Microalbuminuria
Mathiesen et al, 1984	227	70	124±14 / 79±8	131±11 / 85±7
Wiseman et al, 1984	28	30	119±9 / 78±8	135±18 / 86±9
Christiansen & Mogensen 1985	46	15	122±6 / 80±7	133±13 / 88±9

Indeed, we have also observed in the Dallas Prospective Diabetes Trial (130), designed to assess the effect of glycemic control on the progression of microvascular complications, that microalbuminuric patients show a trend to rising blood pressure levels irrespective of glycemic control (Fig 32).

Figure 32 (Ref 130)



The reason for this mild elevation in blood pressure levels associated with microalbuminuria is unclear. Microalbuminuria may indicate renal dysfunction and mesangial expansion of sufficient magnitude to raise the blood pressure. Alternatively, the conventionally accepted normal blood pressure levels may already be too high for a diabetic subject and may account for the increased albumin excretion. Indeed, hypertension by itself can cause increased urinary albumin excretion (131) and antihypertensive therapy has been shown to reduce AER in essential hypertension (132).

Of interest is the study by Christiansen and Mogensen (133) that demonstrates the effect of early antihypertensive therapy in six microalbuminuric diabetic patients with minimally elevated blood pressure levels. Treatment with 100 mg metoprolol twice daily for a mean of 2.6 years reduced blood pressure from 135/93 to 124/84 mmHg and the mean blood pressure from 107 to 97 mmHg. AER decreased from 131 ±2 to 56 ±3 µg/min. GFR was elevated and remained so despite treatment (Table 12.)

Table 12 (Ref 133)

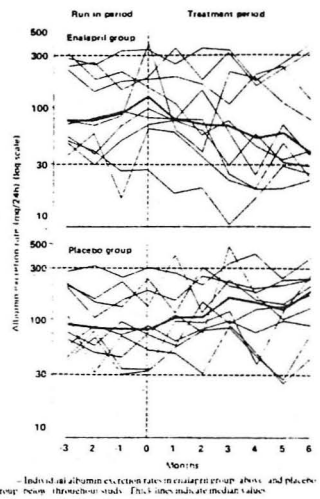
EARLY ANTIHYPERTENSIVE Rx IN MICROALBUMINURIA

	Before Rx	After Rx
Observation Period (yr)	2.6	2.6
Albumin Excretion (μg/min)	131±3	56±4
Blood Pressure (mmHg)	135+9/93±9	124±6/84±3
GFR (ml/min)	149±6	144±11

(From Mogensen and Christensen, Hypertension, 1985)

Recently Marre et al (134) reported a 6 month double blind placebo controlled study of enalapril vs placebo in 20 normotensive diabetic patients with microalbuminuria. Treatment with enalapril decreased the mean blood pressure from 100 to 90 mmHg, whereas no changes were seen in the placebo group. The median AER fell in the enalapril group from 124 mg/24h to 37 mg/24h in contrast to the placebo group showing an increase from 81 mg/24h to 183 mg/24h (Fig 33).

Figure 33 (Ref 134)



It is therefore tempting to speculate that the initiation of antihypertensive treatment at an early stage of kidney disease indicated by rising blood pressure levels and microalbuminuria may prove to have a more effective long term beneficial impact on the progression of diabetic nephropathy than when treatment is started at the overt stage of diabetic nephropathy.

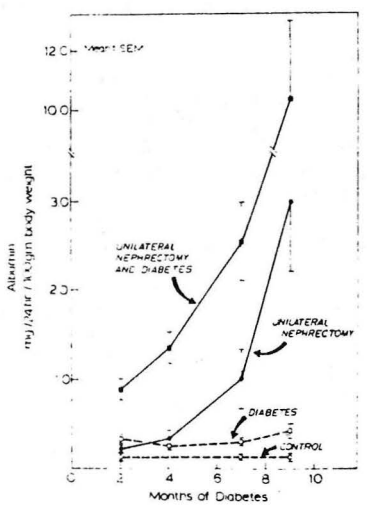
The 1984 report of the "Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure" (135) defines the diagnosis of hypertension in adults as confirmed when the average of two or more diastolic blood pressures on at least two subsequent visits is ≥90 mmHg or when the average of multiple systolic blood pressures on two or more subsequent visits is consistently ≥140 mmHg. It is also stated: "The benefits of drug therapy seem to outweigh any known risks from such therapy for those with a diastolic blood pressure persistently elevated above 95 mmHg and for those with a lesser elevation who are at high risk, i.e., patients with target organ damage, diabetes mellitus, or other major risk factors for coronary heart disease". More recently, the "Working Group on Hypertension in Diabetes" recommended the following: "Considering the additive impact on vascular disease of hypertension occurring in patients with diabetes mellitus, patients with a blood pressure of 140/90 mmHg or greater, should be considered for pharmacologic treatment of mild hypertension if a 3 month trial period of non-pharmacologic treatment of mild hypertention is not effective in lowering high blood pressure (136). Pharmacological management of hypertension in diabetic subjects is different in terms of drug therapy choices, side effects and sequence of antihypertensive therapy and special issues need to be considered (137).

It remains an open question whether conventional levels of hypertension are set too high for potentially reversible diabetic nephropathy and what lower level of blood pressure should be chosen to initiate antihypertensive treatment in patients with diabetes. The presence of diabetes mellitus and the coexistence of microalbuminuria as a marker of initial and progressive target organ damage may justify an aggressive approach to treat blood pressure, perhaps in the level of ≥135/85, in an attempt to stop or retard the progression of the renal disease. Well-designed controlled studies are needed to show whether this aggressive antihypertensive approach has any impact on the course of diabetic nephropathy and also on the morbidity and mortality associated with other cardiovascular conditions.

2. Improved Glycemic Control

Experimental evidence strongly suggest that an abnormal metabolic environment plays a major role in the genesis of diabetic nephropathy. Studies by the Minnesota groups have become classic in support of the effect of glycemic control on diabetic renal lesions. Diabetic glomerulopathy develops in normal kidneys when they are transplanted into diabetic rats (138). Islet cell transplantation in highly inbred diabetic Lewis rats results in marked reduction of immunofluorenscence staining and mesangial volume (139,140). Note the finding that the increased AER seen in intact and uninephrectomized diabetic rats is completely reverted by islet cell transplantation (141) (Fig 34). Similarly, institution of meticulous glycemic control with insulin on streptozocin diabetic rats early in the course of the disease, prevents the development of diabetic glomerular lesions (142-144) and also prevents the increase in AER (145).

Figure 34 (Ref 141)



Urinary albumin excretion in control, diabetic, unilaterally nephrectomized nondiabetic, and unilaterally nephrectomized diabetic rats. In this and the subsequent figures, diabetic animals were given streptozotocin at time 0. On this time scale, uninephrectomy was carried out two weeks later. The two- and four-month time periods include all animals entering the study. Data from those uninephrectomized and intact diabetic animals not receiving pancreatic islet tissue are presented at seven and nine months.

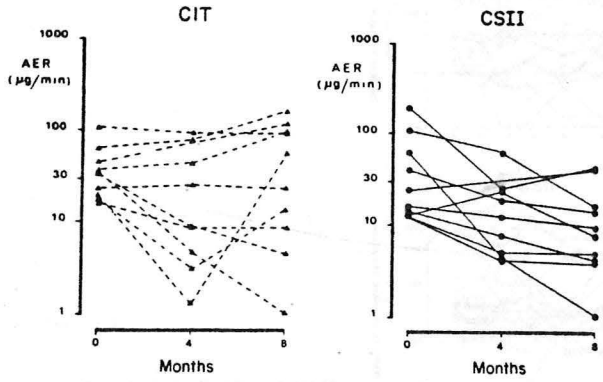
Furthermore, normal kidneys transplanted into human diabetic recipients develop hyaline arteriolar lesions in all renal biopsies in <4 years (146). Mesangial expansion was also noted in several cases. The report of the transplantation of kidneys with clinical diabetic nephropathy into non diabetic recipients caused much controversy. Renal biopsies taken 7 months after the transplants showed that the mesangial expansion and GBM thickness were almost completely reversed (147).

Long term improvement in diabetes control with CSII in six patients with overt diabetic nephropathy proved to be of little value in slowing either the rate of decline in GFR or the plasma creatinine rise seen during the 24 month of intensive therapy (148). The degree of glycemic control achieved might not have been close enough to normal to show an effect; however, near-normoglycemia is very difficult to achieve in patients with diabetic nephropathy (149). Even in the stage of intermittent proteinuria with normal GFR, and normal serum creatinine, near-normoglycemia failed to prevent the decline in GFR or to reduce albumin excretion (150). The main issue appears to be that it is probably too late to attempt to achieve near-normoglycemia when the diabetic nephropathy is clinically established. Advanced renal lesions are already present, and the process may have become self-perpetuating.

Glycemic control, as assessed by glycosylated hemoglobin levels, correlates with the AER in early diabetic nephropathy (73). Initial reports seemed to indicate that short and relatively long term near-normoglycemic control achieved with CSII was an effective strategy to reduce and sometimes reverse microalbuminuria (151-154). However subsequent studies demonstrated that the impact of near-normoglycemia is at best manifested by slowing down the progression of microalbuminuria (130,155,156). It now appears that once persistent microalbuminuria develops, improved glycemic control can not reverse it.

The Kroc multicenter study initially found a beneficial effect on near-normoglycemia on microalbuminuria (154). Complete 24h urine collection were obtained throughtout the 8 month study in 59 of the 68 IDDM patients. At baseline, the AER was normal (<12 µg/min) in 39 patients, 20 receiving conventional insulin treatment and 18 on CSII, and above normal in the other 20 patients (10 patients in each group). In the patients with normoalbuminuria, AER was relatively constant regardless of the type of treatment. However, patients on CSII with an elevated AER had a progressive decline in albumin excretion from 48 ± 5µg/min at 8 months. In contrast, the elevated AER in the conventional treatment group remained unchanged (Fig 35). The main objection to this study is that baseline urinary albumin consisted of only a single sample that could have reflected the poor glycemic control before the CSII treatment. Several urine samples are usually required to define persistent microalbuminuria characteristic of early diabetic nephropathy.

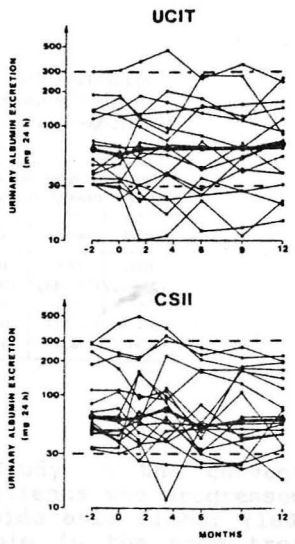
Figure 35 (Ref 154)



Effect of treatment on albumin excretion in patients with microalbuminuria in KROC study. CIT, conventional therapy; CSII, continuous subcutaneous insulin infusion.

The Steno Memorial Hospital also reported the effect of 6 months of strict metabolic control on kidney function in 32 IDDM patients randomized either to unchanged conventional treatment (UCT) or to CSII (152). HbA$_1$C was unchanged in the UCT, around 8%, but fell significantly to 6.7% in the CSII treated group. AER fell by 12% with CSII and rose by 56% with UCT. Subsequently, the same study group reported results of the 2 year follow-up study on the effect of near-normoglycemia on kidney function (153). AER remained unchanged during CSII in 12 of 13 patients with initial AERs $\leq$70 µg/min. Only 1 of the 3 microalbuminuric patients (>70 µg/min) in the CSII group progressed to overt proteinuria, whereas all 5 microalbuminuric patients in the UCT group progressed to persistent proteinuria. Subsequently the Danish extended their observations in a careful study specifically designed to assess the impact of strict glycemic control on kidney function in IDDM patients with persistent microalbuminuria (155). Patients selected for the study had two of 3 24h dipstick-negative urine collection with an AER between 30 and 300 mg/24h (20-200 µg/min). Thirty six patients were matched in pairs according to the level of AER, sex, and HbA$_1$C before random assignment to either UCT or CSII. Despite a significant reduction in HbA$_1$C (from 9.5 to 7.3%) in the CSII group, their first report after 1 year of follow up, showed that the AER remained constant in both groups (Fig 36), GFR was unchanged, and kidney size was significantly reduced in the CSII group.

Figure 36 (Ref 155)



Urinary Albumin Excretion in the First Year during Unchanged Conventional Treatment (UCIT) and during Continuous Subcutaneous Insulin Infusion (CSII).

These later changes in GFR and kidney size were in direct opposition with the report by Wiseman et al (157), who showed that prolonged (1 year) correction of hyperglycemia with CSII can reduce the GFR in IDDM patients with persistent glomerular hyperfiltration. In the Wiseman study the GFR was reduced well into the normal range in most cases. A return to conventional insulin treatment in the pump group resulted in both metabolic deterioration and a significant rise in the mean GFR toward baseline values. No change in kidney volume was noted, and the AER was normal in all the patients on CSII, whereas on the conventional group, 3 patients had elevated AER. No significant changes in AER was detected in either group during the study.

In terms of developing diabetic kidney disease, more prolonged observation will be required to properly assess whether near-normoglycemia can prevent further progression of diabetic nephropathy. Hopefully after several years the two therapeutic groups will separate, assuming that the AER continues to rise in the UCT group and at least remains stable in the CSII group. However, it was most surprising that it only required an additional year of observation for the Steno study to show, what they interpreted as a beneficial effect of near-normoglycemia on the annual increase in AER. In their second report after 2 years of follow up, clinical diabetic nephropathy (urinary albumin excretion rate >300 mg/24h) developed in 5 patients in the conventionally treated group but in none of the CSII group (156). The fractional albumin clearence increased in the conventional treatment group and remained unchanged in the CSII group (Table 13).

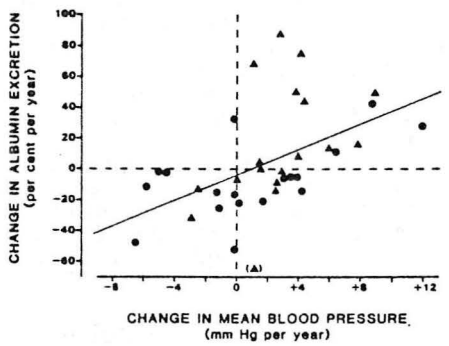
Table 13 (Ref 156)

—EFFECT OF CONTINUOUS SUBCUTANEOUS INSULIN INFUSION (CSII) OR UNCHANGED CONVENTIONAL INSULIN TREATMENT (UCIT) ON BLOOD GLUCOSE LEVELS AND FRACTIONAL ALBUMIN CLEARANCE

Treatment group	Mean (SEM) blood glucose (mmol/l)*			Median (range) fractional albumin clearance × 10⁷‡		
	0 mo	12 mo	24 mo	0 mo	12 mo	24 mo
CSII (n = 18)	10·0 (2·0)	7·0 (1·0)†	6·5 (0·7)†	170 (31–608)	190 (24–753)	160 (26–460)
UCIT (n = 18)	11·3 (2·0)	10·2 (2·0)	10·5 (1·1)	160 (35–468)	210 (33–594)	360 (29–1580)
CSII *v* UCIT	NS	$p < 0.05$	$p < 0.05$	NS	NS	NS

More careful analysis of this study in the conventional treated group revealed that those 5 patients who progressed, had a mean baseline microalbuminuria considerable higher (189 ± 61 mg/24h) than those who remained stable in the same treatment group (51 ± 24 mg/24h). Of note is that the diastolic blood pressure rose significantly only in the conventionally treated group. The annual change in urinary albumin excretion correlated with the annual change in mean blood pressure. Furthermore, all 11 patients in the conventional hyperglycemic group whose AER showed a rising trend also had rising blood pressures (Fig 37).

Figure 37 (Ref 156)

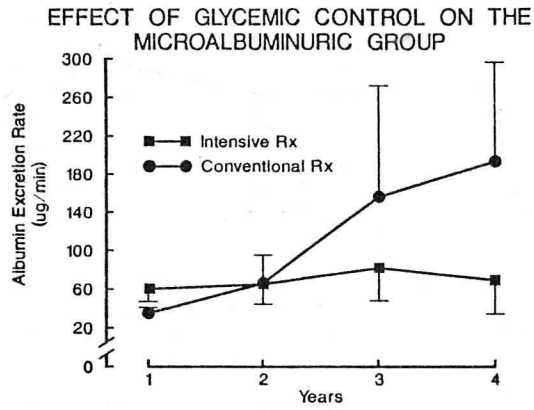


—Correlation between annual change in mean blood pressure and annual change in urinary albumin excretion.

We have also observed that microalbuminuric patients with near-normoglycemic control showed no signs of progression in

urinary AER as compared with hyperglycemic conventionally treated microalbuminuric patients over a 3 year follow-up period (Fig 38). As mentioned above, a trend for rising blood pressure levels were seen in both microalbuminuric groups. Near-normoglycemic control seems not to reverse established microalbuminuria but may prevent the progressive increase in urinary AER seen in conventionally treated Type I diabetic patients (130).

Figure 38 (Ref 130) **DALLAS DIABETES PROSPECTIVE TRIAL**



To sum up, improved glycemic control seems a reasonable approach as part of a comprehensive therapeutic strategy that also includes blood pressure lowering measures. It must be remembered that intensive diabetic treatment is very expensive both to the patient and to the health care system (158,159). The ever present danger of insulin-induced hypoglycemia with potentially lethal consequences also exists, and indeed is increased threefold as demonstrated by the DCCT trial (160). Thus, given both the risks of aggressive insulin therapy and the considerable ambiguity of the evidence discussed above, we strongly believe that results of a large scale clinical trial are needed to define the microalbuminuria issue more clearly. The Diabetes Control and Complication Trial (160) is such a trial and it is well underway.

3. Low Protein Diets:

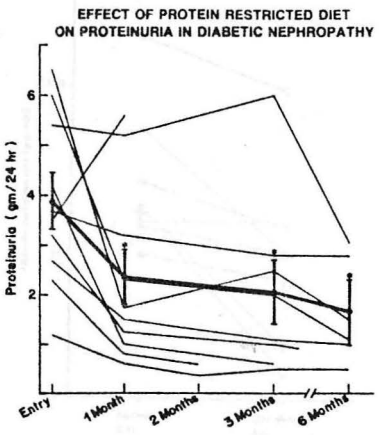
Dietary intervention with low protein diets has long been recommended in patients with chronic renal failure (161). Several studies have shown that protein restricted diets slow the progressive decline of renal failure and prolong life in patients with moderate to severe renal disease (161-164). The rationale for this dietary approach is based on early

experimental evidence that high-protein diets accelerate the glomerular lesions in intact and uninephrectomized rabbits or rats (165-168). Conversely, low-protein diets appear to retard the progression of nephrotoxic serum nephritis in rats (169).

The mechanisms involved in the hyperfiltration associated with high protein diets remain unknown, but may be determined by alterations in the tubuloglomerular feedback system (170). Protein restriction is clearly effective in preventing the hyperfiltration and renal pathologic changes occuring in the remnant glomeruli of rats with reduced renal mass (91, 94). Brenner and colleagues (171,172), and Jamison (173) have reconciled the hyperfiltration model of the "remnant kidney" with the chronic effects of excess protein intake on the progression of renal disease. This theory proposes that an increase in protein intake causes renal vasodilation and glomerular hyperperfusion eventually disrupts the glomerular permselectivity and causes albuminuria with subsequent mesangial expansion. As discussed above, the same model of glomerular hyperfiltration has been proposed by those authors to explain the genesis of diabetic nephropathy (93). Note the report by Neugarten et al (174) that streptozocin diabetic rats fed high protein diets (50%) have an acceleration of diabetic nephropathy as evidenced by greater mesangial expansion and GBM thickening as well as higher proteinuria than diabetic rats with 20% protein chow. Similar findings were subsequently confirmed by Zatz et al (94), as discussed above.

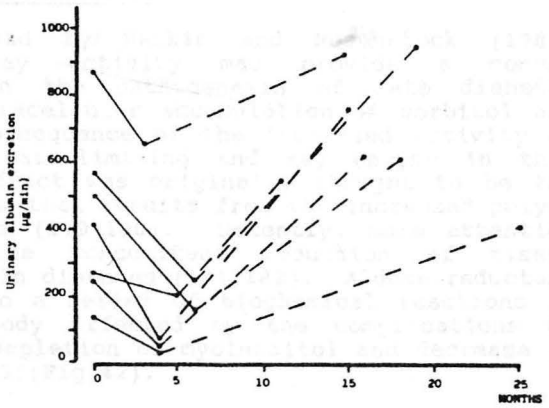
K. Zeller (175) is currently conducting a carefully designed long term study to assess the effects of low protein diets (0.6 g/k/day) on an homogeneous population of patients with advanced diabetic nephropathy. Figure 39 shows preliminary data suggesting that dietary protein restriction significantly reduces proteinuria, but more prolonged observation is needed to determine whether the course of diabetic nephropathy is indeed retarded.

Figure 39 (Ref 175)



Recently Ciavarella et al (176), reported the effects of a 5 month low protein diet (0.7 ± 0.1 g/kg/day) on 7 Type I proteinuric patients with levels of serum creatinine between 0.7 - 1.9 mg/dl. A significant reduction from 434 ± 244 to 205 ± 212 µg/min in AER was found in all patients on the low protein diet compared to those 9 control patients on 1.4 ± 0.1 g/kg/day protein diet. Upon discontinuation of the low protein diet, a significant reincrease in AER was observed (Fig 40).

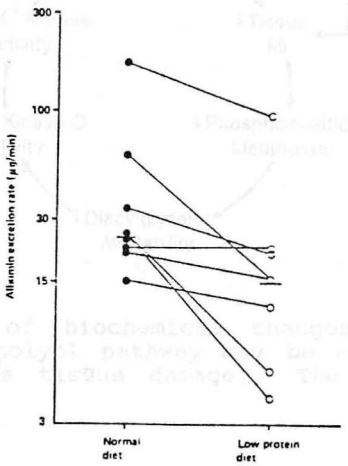
Figure 40 (Ref 176)



Decrease in albumin excretion during low-protein diet (*solid lines*) (average 4.5 mo) and reincrease (*broken lines*) in albumin excretion during subsequent period (average 9.5 mo) of normal diet in same group.

The only report in microalbuminuria is from Cohen et al, (177) who conducted a short term 3 week crossover study in 8 microalbuminuric patients given an average 47 and 92 g/day protein diet. Overnight AER fell from 23 µg/min to 15 µg/min on the low protein diet (Fig 41).

Figure 41 (Ref 177)

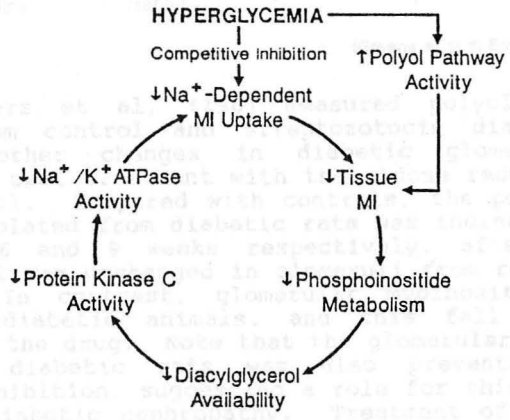


No long term studies are available on the potential beneficial effect of low protein diets on microalbuminuria in patients with early diabetic nephropathy. Low protein diets seem like a "healthy" and "non invasive" intervention that require proper validation. Even if this is accomplished, the magnitude of the effect is not very impressive and compliance is a major problem. Nonetheless, it is a sensible approach, perhaps unrealistic, that may find some value as an adjunt rather than as a primary line of intervention.

4. Aldose Reductase Inhibitors

As recently reviewed by Raskin and Rosenstock (178), enhanced polyol pathway activity may provide a common biochemical vinculum in the pathogenesis of late diabetic complications. The intracellular accumulation of sorbitol and fructose occurs as a consequence of the increased activity of aldose reductase, the rate-limiting and key enzyme in this pathway. An osmotic effect was originally thought to be the main pathogenic mechanism that results from the increased polyol concentration in tissues (179,180). Recently, more attention has been given to the concomitant reduction of tissue myoinositol levels seen in diabetes (181,182). Aldose reductase activation is coupled to a series of biochemical reactions in many tissues of the body affected by the complications of diabetes, resulting in depletion of myoinositol and decrease in Na-K ATPase activity (183)(Fig 42).

Figure 42 (Ref 183)



These series of biochemical changes that result from activation of the polyol pathway may be a mechanism by which hyperglycemia causes tissue damage. The presence of aldose

reductase activity has been clearly documented in retina, lens, Schwann's cell, aorta, and also in glomerular tissue (178). Administration of an aldose reductase inhibitor (ARI) ameliorated the diabetes related changes in nerve sorbitol and myoinositol and improved nerve conduction velocities in rats (184) and humans (185) with an apparent beneficial effect in painful diabetic neuropathy (186-188). In addition, experimental evidence has also shown that aldose reductase inhibitors prevent cataract formation (180) and, more importantly, prevent galactose-induced retinopathy with striking reduction in retinal capillary basement membrane thickness (189). Table 14 summarizes the experimental findings with ARI in tissues susceptible to diabetic complications.

Table 14 (Ref 183)

TISSUES DEPLETED OF MYOINOSITOL IN RESPONSE TO HYPERGLYCEMIA

Tissue	Species	Inhibition MI Uptake by Glucose	Prevention Aldose Reductase Inhibitor	Decrease Na-K ATPase Activity
Sciatic Nerve	Rat	Yes	Yes	Yes
	Rabbit	Yes	Yes	Yes
	Human	?	?	?Yes
Autonomic Ganglion	Rat	Yes	Yes	Yes
Renal Glomerulus	Rat	Yes	Yes	Yes
Retina	Rabbit	?	?	Yes

(Greene et al, N Eng J Med 1987)

Beyer-Mears et al, (190) measured polyols in glomeruli isolated from control and streptozotocin diabetic rats and assessed whether changes in diabetic glomeruli could be prevented by oral treatment with the aldose reductase inhibitor drug, sorbinil. Compared with controls, the polyol content of glomeruli isolated from diabetic rats was increased 10 fold and 4 fold at 6 and 9 weeks respectively, after induction of diabetes. It was unchanged in glomeruli from rats treated with sorbinil. In contrast, glomerular myoinositol content was reduced in diabetic animals, and this fall was completely prevented by the drug. Note that the glomerular accumulation of protein in diabetic rats was also prevented with aldose reductase inhibition, suggesting a role for this pathway in the genesis of diabetic nephropathy. Treatment of streptozotocin-diabetic rats with sorbinil reduces proteinuria and restores the urine electrophoresis pattern towards normal (191). Of great interest are the preliminary reports indicating that administration of aldose reductase inhibitors can reduce the increased GFR seen in streptozotocin diabetic rats (192). Similar effects on GFR were demonstrated in the same animal

model with the use of diets supplemented with myoinositol (192,193).

If this enzymatic pathway does serve as some pathogenic mechanism in all or some of the diabetic complication, then the inhibition of aldose reductase may represent a direct pharmacologic approach in the treatment of certain diabetic complications. This approach is distinct and separate from treatments designed to improve blood glucose levels. To date no human studies have been reported on the potential beneficial effect of aldose reductase inhibitors on either overt proteinuria or on the microalbuminuria of early diabetic nephropathy.

V. CONCLUSION

The natural history of early diabetic nephropathy remains to be further elucidated. Glomerular structural and hemodynamic changes seem important, however, the precise pathophysiological events leading to microalbuminuria are still unclear.

Interpretation of the evidence presented, supports the notion that microalbuminuria, rather than being a "predictor of future diabetic nephropathy", is indeed a "marker of incipient hypertension" that seems to warrant intervention. Endless discussions on what comes first, the hypertension or the renal disease, can be predicted!

In addition to the ongoing DCCT study evaluating the role of glycemic control on diabetic complications, we clearly need a long term controlled prospective study to assess lower blood pressure goals on the rate of progression of diabetic nephropathy. Although perhaps premature, my feeling about the role of blood pressure in the development of diabetic renal disease is much the same as the role of cholesterol levels in the development of atherosclerosis: "The lower the better".

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