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Reviews

Microalbuminuria, blood pressure and diabetic renal disease: origin and development of ideas

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Introduction

Microalbuminuria and diabetic renal disease are closely linked [1–14] and are associated with hypertension and often antecedent hyperfiltration [1]. Microalbuminuria usually indicates the beginning of diabetic nephropathy as opposed to overt nephropathy characterized by clinical proteinuria according to generally defined standards [14–15] but it has an even broader impact because it is also often found in essential hypertension as first described by Parving et al. [16]. This indicates that it is involved in early renal and vascular disorders which can predict advancing renal disease as well as the progression of cardiovascular disease [17]. This concept of prediction however is becoming increasingly difficult to pursue because many patients are treated with anti-hypertensive drugs and other types of interventions when microalbuminuria is diagnosed; such measures often return albumin excretion to normal [17–19]. Further in population-based studies microalbuminuria is not uncommon, especially in elderly people where it is also strongly related to cardiovascular disease and mortality, as in both in Type I (insulin-dependent) and Type II (non-insulin-dependent) diabetes mellitus [20–29]. Whether it should be considered as a part of the metabolic syndrome is still doubtful as it relates more specifically to high blood pressure and glucose intolerance [30]. In diabetic pregnancy, an increase of microalbuminuria predicts complications [7, 31].

Thus microalbuminuria can be considered as an early sign of damage not only of the kidney but also the cardiovascular system [17, 18, 28, 32]. For intervention strategies to prevent or reverse the abnormality, also in terms of hard end-points, it is crucial to define and recognize pathogenetic risk factors involved in the aetiology of disease [33–41]. It is, however, equally important to consider early signs of disease because microalbuminuria usually indicates detectable renal structural damage [42–49]. If we can diagnose and intervene with effective strategies at an earlier stage, e.g. by hyperfiltration [50–56] or guided by provocation tests [57, 58] or with very early risk factors we might be able to further improve prognosis. Very early risk factors to be considered could be pre-natal, such as genetic elements, birth-weight and familial predisposition to renal and vascular disease.

The interrelation of risk factors seems to some extent, however, to have confused the medical community for years. This also applies to the real pathogenetic importance of hyperglycaemia per se, not only because of poor recognition of hyperglycaemia before the HbA_{1C}-era, but also the failure to recognize that the two important risk factors, high blood pressure and increased blood glucose concentrations, must be considered together. These are fundamental risk factors for cardiovascular disease also, and in diabetes, hyperlipidaemia could be of equal or even greater importance [59]. Considered together, the

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Abbreviations: GFR, Glomular filtration rate; ACE, angiotensin-converting enzyme.

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Table 1. Studies related to nephromegaly, hyperfiltration and microalbuminuria

Phenomenon	Nephromegaly	Hyperfiltration	Immune measurement of albumin	Microalbuminuria Type I diabetes
Early observation	Paris 1849 C. Bernard [62]	Belgium/Italy Switzerland [276–278]	Sweden [99]	London, Aarhus [100, 283, 284]
Subsequent studies and observations	Several pathologists [63]	Denmark [279, 280]	London, RIA [282]	Follow-up: London, Copenhagen Aarhus [73, 105, 106]
Newer studies	Aarhus 1973 [67, 68] Copenhagen 1991 [275]	Boston [70] Stockholm [71] London [281]	Aarhus [283, 284]	Many studies [290]
Confirmed and/or clinical significant	Munich 1998 [69]	Confirmed but clinical assessment too cumbersome	Rapid procedures Aarhus [102–104], Guidelines [285–287]	Several guidelines [287, 288, 291]

Table 2. Glomerulopathy, epidemiology, syndrome X and significance of near normal glycaemia

Phenomenon	Glomerulopathy and proteinuria	Epidemiology of micro-albuminuria and mortality (incl. Type II diabetes)	Metabolic syndrome or syndrome X	Significance of glycaemic control
Early observation	Kimmelstiel and Wilson, 1936 [292, 293]	London, Epidemiology [100] Aarhus, Mortality [112, 113]	Sweden 1923 [140] England 1939 [141] France 1949 [142, 143] Italy 1965 [144]	Keiding 1952 [300] Providing the concept Pirart 1978 [84]
Subsequent studies	Several pathologists [294–297]	Aarhus [116] Fredericia [20] London [27]	Ferranini [32] Reaven [299] Hoorn Study [30]	Scandinavia [301] Gothenburg [222]
Newer studies	Aarhus/Minneapolis (Morphometry) [47, 298] Japan [127]	Mortality data firmly confirmed [113]	Concept used by many investigators	DCCT [41] Oslo/Aarhus [48] Gothenburg [302] Copenhagen [15]
Confirmed and/or clinical significant	Several reviews [147, 291]	Used now in all epidemiol-ogical and large trials	Still ill defined [145] Not measured clinically	Several guidelines (widely accepted)

long-term occurrence over the years of high blood glucose and high blood pressure is highly indicative of the development of renal disease, other microvascular lesions and also macrovascular disease. Conversely, low blood pressure can be protective, even with long-standing diabetes and poor glycaemic control. Another confounding issue has been the seemingly independent development of retinopathy and renal disease in some situations. Some studies have failed to recognize that morphological diagnosis of renal disease is often lacking in epidemiological studies, by contrast to retinopathy, although clinically meaningful microvascular disease usually develops in a very concordant fashion [60, 61].

This review discusses how pertinent concepts of diabetic renal disease have developed over the years (Tables 1–4). It also focuses on earlier diagnosis based on exact measures such as ambulatory blood pressure, provocation test and precise monitoring of glomular filtration rate (GFR) as well as other renal function tests to define the earliest possible stage predictive of incipient or overt disease (Table 5). Several new theoretical concepts are mentioned briefly (Table 6) and potential end-points are discussed (Table 7).

Nephromegaly and hyperfiltration

The origin of ideas often goes much further back than investigators in the research field generally acknowledge. Thus, nephromegaly had been observed more than a century before it was rediscovered. C. Bernard [62], with quite another purpose in mind, observed pronounced nephromegaly in a patient with newly diagnosed diabetes who was in the care of M. Rayer in a Parisian Hospital in the 1840s and was examined after a sudden and unexpected death. The nephromegaly seen in the post mortem examination corresponds closely with new observations (Fig. 1). Between 1848 and 1974 nephromegaly was not broadly recognized clinically, although it seemed to be a common finding among pathologists [63]. It was described in textbooks in France even before C. Bernard [64, 65]. New observations indicated considerable renal enlargement in experimental diabetes [66]. Nephromegaly was proposed as an index of long-term glycaemic control and could thus theoretically be used to document a possible relation between hyperglycaemia and later overt nephropathy [67–68]. This concept was recently further elaborated by the

Table 3. The concept of renoprotection

Phenomenon	Protection by AHT Incipient nephropathy (Type I)	Protection by AHT Overt nephropathy (Type I)	Protection by AHT in Microalbuminuria (Type II)	ACE-I and renal protection
Early observation	Aarhus 1985 [190]	Aarhus 1976–1982 [208, 211]	Israel [200, 201]	Boston, experimental [239, 307]
Subsequent observation	Paris [195] Copenhagen [196, 197] Melbourne [198]	Copenhagen [212–216] Goethenburg [217]	Melbourne [198] Several studies	Aarhus [308] Paris [195] Copenhagen [197] Melbourne [198]
Newer studies	Euclid [203, 303] Aarhus [177] Italy [304]	Many studies [219]	Several studies [305]	UKPDS (probably similar effect with beta-blockers) [131]
Confirmed and clinical significant	Several guidelines [287]	Several guidelines [287]	Clinically used [305] Multifactorial intervention important [306]	Maybe more effective than ordinary AHT [15]

AHT, antihypertensive treatment

Table 4. Pathophysiological and genetic studies

Phenomenon	Complication genetically or metabolically determined	Provocation tests (e.g. exercise)	24 h-amb. BP in diabetes	Dextran and PVP clearance
Early observation	Siperstein 1973 [82]	Karlefors [146]	Rubler, 1982 [160]	Uppsala [180]
Subsequent observation	Deckert [83] Aarhus [42]	Aarhus [150]	Aarhus [161]	Düsseldorf [181] Aarhus [2, 72] Liège [182]
Newer studies	London [309] Boston [310] Copenhagen [86] France [311]	Only few studies [177, 312, 313]	Several studies [175]	Copenhagen [183] San Francisco [184]
Clinical significance	My present view: Renal complication mainly metabolically determined and modulated by hypertension	Not widely used, but may be relevant in treatment trials [177, 314]	Should be used more (Guidelines elaborated) [175]	Little used [2]

PVP, polyvinyl-pyrrolidin

observation that diabetic patients with extreme nephromegaly were at greater risk of developing overt renal disease [69].

The functional abnormality, to some extent concomitant with nephromegaly, is hyperfiltration and intrarenal hypertension which have been originally proposed to be of key pathogenetic relevance by Brenner and this group [70]. Studies in diabetes indicate that hyperfiltration is of considerable importance [56] as evidenced by several follow-up studies, most convincingly by Rudberg et al. [71]. Some studies have failed to document correlations possibly because of too broad inclusion criteria, e.g. patients with newly diagnosed diabetes before insulin treatment [56]. These patients are known to have pronounced hyperfiltration that can be reversed with treatment [72]. The predictive role of hyperfiltration could be difficult to study now, because there is a more intensified control in diabetes, both before and after the development of microalbuminuria. Even so, hyperfiltration, associated with microalbuminuria and slightly raised blood pressure [73], is likely to be strongly predictive of renal disease, perhaps to some extent because hyperfiltration in parallel to nephromegaly is related to poor metabolic control [68, 74]. In contrast to microalbuminuria, hyperfiltration and nephromegaly are, however, rarely included in

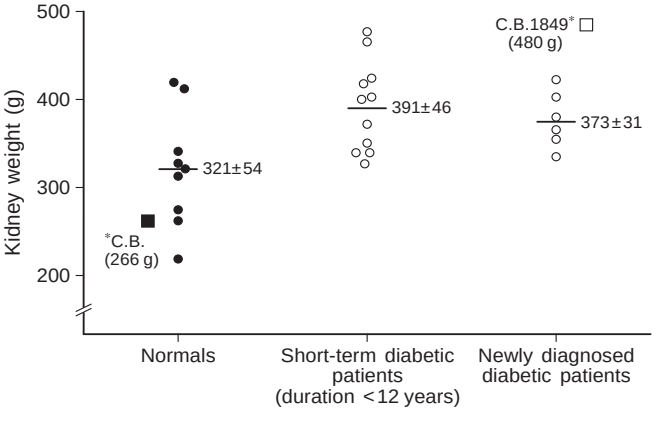

Fig. 1. Kidney weight in normal and diabetic subjects. *Reference [62, 67, 68]

Table 5. Stages in the development of renal changes and lesions in diabetes mellitus (Type I)

Stage	Chronology	Main structural changes or lesions	Glomerular filtration rate	Dextran clearence (% of GFR)	Albumin excretion		Blood pressure	Reversible by strict insulin treatment	Arrestable or reversible by AHT
					Baseline UAE[a]	Exercise-induced UAE			
1 Acute renal hypertrophy-hyperfunction	Present at diagnosis of diabetes (reversible with good control)	Increased kidney size. Increased glomerular size	Increased by 20–50 %	Normal	Maybe increased, but reversible	Increased, but reversible	Normal	Yes	No hypertension present. Microcirculatory changes modifiable
2 Normoalbuminuria (UAE < 20 μg/min)	Almost all patients normoalbuminuric in first 5 years	On renal biopsy, increased BM thickness	Increased by 20–50 %	Normal	Normal by definition (15–20 μg/min maybe abnormal)	Maybe abnormal after a few years	Normal (BP as in background population) Increase by 1 mmHg/year	Hyperfiltration reduced	Filtration fraction and UAE maybe reduced
3 Incipient diabetic nephropathy, UAE 20–200 μg/min	Typically after 6–15 years (in ≈ 35 % of patients)	Further BM-thickening and mesangial expansion, arrestable with AHT[d]	Still supranormal values, predicted to decline with development of proteinuria	Normal	Increase: ≈ 20 %/year (of glomerular origin)	Abnormal aggravation of baseline UAE, related to BP-increase	Incipient increase, ≈ 3 mmHg/year (if untreated)	Microalbuminuria stabilized, GFR also stable (*if* HbA_{1c} *is* reduced). Structural damage slower	Microalbuminuria reduced. Prevention of fall in GFR Arrestable by AHT[d]
4 Proteinuria, clinical overt diabetic nephropathy	After 15–25 years (in ≈ 35 % of patients)	Clear and pronounced abnormalities	Decline ≈ 10 ml/min/year with clear proteinuria[c]	Abnormal to high mol dextrans (non-specific and only with low GFR)	Progressive clinical proteinuria[c] of glomerular origin	Pronounced increase in BP	High BP, increase by ≈ 5 mmHg/year (if untreated)	Higher fall in GFR with poor control	Progression reduced (aiming at 135/85 mmHg)
5 End-stage renal failure	Final outcome, after 25–30 years or more	Glomerular closure and advanced glomerulopathy	< 10 ml/min	Not studied	Often some decline due to nephron closure	Not studied	High (if untreated)	No	No

BM = Basement membrane; UAE = urinary albumin excretion rate; AHT = antihypertensive treatment
[a]The best clinical marker of early renal involvement; [b]Mostly ACE-inhibition + diuretics; [c]Without antihypertensive treatment
The classification was conceived and presented on ideas presented in ref. 2, and updated – based on studies 1983–1998 [2, 14]. [d]Personal communication, Rudberg and Østerby

Table 6. Newer therapeutic concepts

	Aldose-reductose inhibition	Selective growth factor inhibition	Selective protein-kinase-C inhibition	Angiotensin receptor blockade	AGE-inhibition
Theoretical, basis, reference	Mau Pedersen [51]	Flyvbjerg, Ziyadeh [315, 316]	Koya and King [317]	Hollenberg [318]	Cooper and Jerums [319]
Human studies	Mau Pedersen [51, 52]	Few, Mau Pedersen [50]	In progress	Many important studies conducted and in progress [247, 248]	?
Clinically used	No	Not yet	No	Widely used	No

Table 7. The endpoint: GFR-decline rate related to intermediary end points in diabetic patients

Intermediary end points	GFR-decline (Young Type I diabetic patients)	GFR-decline (Middle-aged Type II diabetic patients)
Microalbuminuria[a] (20–200 μg/min)	Decline in GFR[a] only seen with progression to proteinuria	Decline rate of GFR[a] usually not noteably different from normoalbuminuria
Proteinuria[b] (macroalbuminuria, > 200 μg/min)	Clear decline in GFR[b]. (Reduced by antihypertensive treatment)	Clear decline in GFR[c]. High mortality
Blood pressure[b]	Controversy exists but a clear risk factor with co-existing abnormal albuminuria	Controversy exists but a clear risk factor with co-existing abnormal albuminuria

Related to future mortality and ESRD with increasing power ([a]) ([b]) ([c]).
ESRD, end-stage renal disease

the clinical evaluation of patients, partly because their relevance under routine circumstances can be difficult to ascertain as the procedures involved are technically too demanding in a busy clinic. Regarding mechanisms, atrial natriuretic peptide could be involved both in hyperfiltration [74] and microalbuminuria [75, 76]. The genesis of hyperfiltration is, however, likely to be multifactorial [77].

Genetic or familial factors

It has been suggested that there is a discrepancy between the development of renal disease and retinopathy in that retinopathy is much more common than nephropathy. It has possibly not been taken into consideration that the diagnoses of retinopathy is most often based on retinal photographs, that is morphology. By contrast renal disease is diagnosed by the occurrence of microalbuminuria or proteinuria and only rarely through renal biopsies. With morphological diagnosis the prevalence of the two microvascular lesions could be very similar. Actually, as shown by the Melbourne group, development of clinically important renal disease is strongly associated with the occurrence of retinopathy [60, 61]. Thus, the basis for considering susceptibility factors distinct from the development of renal disease and retinopathy could be weakly founded. In Type II diabetes the degree of retinopathy might be seen later but it clearly correlates with that of glomerulopathy [78]. It is nevertheless still surprising and so far unexplained that some Type II patients have proteinuria, but not retinopathy, according to standard evaluation [78].

Another key issue is that more than one risk factor must be present for the development of apparent clinical disease. Thus isolated hyperglycaemia might not suffice to develop overt renal disease, whereas two co-existing risk factors namely, hyperglycaemia and high blood pressure, must be present as underscored in the UK prospective diabetes study [79, 80]. Conversely the development of microalbuminuria is usually accompanied by the development of increased blood pressure. Therefore, there should be recognition of both risk factors. In long-term studies, in diabetic patients without clinically meaningful microvascular lesions, blood pressure is lower than in the general population which again supports the prerequisite of at least two risk factors in the genesis of renal disease [81].

Interestingly, clinical management was hampered for many years by the studies of Siperstein and coworkers [82] suggesting that morphological lesions can be present at or before the clinical diagnosis of diabetes. This would lend some support to genetic factors being decisive for the development of microvascular disease. A tempting, but dangerous conclusion would then be that the development of microvascular lesions is not responsive to better metabolic control but related to genetic "destiny" rather than to treatment failure [83]. These concepts were incorrect, at least for the kidney, as substantiated by the studies by R. Østerby who showed that structural lesions develop after diabetes has been present for some years [42–48]. Muscle basement membrane might be less suited to measurement [49].

In his long-term follow-up studies Pirart showed that for microvascular lesions and neuropathy, gly-

caemic control was important [84]. Several European intervention studies confirm the correlation between hyperglycaemia and the development of renal disease [85]. It was not, however, until the Diabetes Control and Complications Trial (DCCT) [41] was completed that this was widely accepted in the United States, an attitude which, in retrospect, could in many places have had a deleterious effect on clinical management before 1993. This could also apply to the management of Type II diabetic patients, in whom metabolic control quite often is not perfect, but this will possibly change after publication of the UK prospective diabetes study [79].

Studies on genetic predisposition should be considered in the context of several risk factors [15]. Thereby certain angiotensin-converting enzyme (ACE) genotypes have been shown to possibly affect progression [86], although data are diverse and might not relate to all Western populations [87, 88] as the effect can possibly only be seen in large meta-analyses [86]. In Type II diabetes there seems to be no such effect in Caucasians [86]. Familial predisposition to hypertension, also seen in affected patients, could still be important in a concordant, yet multifactorial, fashion [89, 90] and blood pressure can be treated once the patients become hypertensive. Recent work also suggests some racial and familial clustering of renal disease in black patients [91–92] but often such patient-material is small and familial clustering of environmental factors are just as likely [93].

Birth weight, hypertension and microalbuminuria

It has been suggested that low birth weight could be predictive of cardiovascular renal disease in diabetes and in the general population [94]. Small kidneys could relate to fewer glomeruli and an increase in the pressure gradient in existing tissue. This concept was not, however, supported by our studies on the relations between birth weight, renal and glomerular size [95, 96]. Also in population-based studies we failed to find any correlation between microalbuminuria or raised albumin secretion and birth weight. Nor was there any correlation between blood pressure and birth weight [25]. Therefore it seems inconceivable that pathologically low birth weight could be an important determinant of essential hypertension or associated renal disease, in particular, because hypertension is highly prevalent in the Western population and found in perhaps 15–20 % of elderly people. Hypertension is more closely related to actual increased body mass index or abdominal adiposity. A relation between low birth weight and the development of diabetes and some element of cardiovascular disease might however exist, although it is not consistent, is possibly weak, and is not relevant in the management of patients [97, 98].

Immune-based measurement of albumin in low concentrations

Progress in medical research is often driven by new methodology and procedures, e. g. by more sensitive techniques. This was the case with the study of early development and early treatment of diabetes associated renal disease. The first study describing measurements of albumin in normal urine was quite elaborate requiring pre-concentration of urinary albumin [99]. This completely changed after the introduction of radioimmuno assays for albumin that often even required dilution of urine samples and led to the term microalbuminuria [100]. The introduction of such methods was important in the study of the early diabetes-associated renal impairment in cross-sectional and longitudinal studies. Radioimmuno assays were, however, still laborious and time-consuming for clinical use and therefore it was an important step forward when immuno-turbidimetry and other immune precipitation tests were developed; this allowed processing of multiple samples of urine at high speed for use in clinical practice [12]. It was a major step forward in the clinical management of patients with diabetes and also those with essential hypertension [17, 101].

Clinical management has benefited further from the introduction of effective and quick bedside and dipstick tests for measurement of albumin. The introduction of the Micral 1 and Micral 2 tests which are not quantitative was of major benefit [102, 103], with the Micral 2 test being very efficient and easy to use in the clinic [103].

In our clinical laboratory a very good quantitative correlation has been obtained through the measurement of the albumin:creatinine ratio by the DCA2000 apparatus compared with measurement by immuno-turbidimetry [104]. Thereby it is possible to rapidly measure not only HBA_{1C} but also albumin and creatinine [104], an ideal situation for small clinics where large-scale measurements of these compounds are not always necessary. We have thus experienced huge progress in our laboratory techniques from the initial extremely laborious methods in the early 1960 s [99] to the very quick and efficient bedside tests of the 1990 s [104].

Microalbuminuria in Type I diabetes

Three independent groups have consistently shown that microalbuminuria predicts overt renal disease [73, 105, 106]. Consequently it is now wide-spread clinical practice to screen for microalbuminuria, especially as it has subsequently been shown that intervention is effective (as described later). Follow-up studies of initial cohorts have also shown that microalbuminuria is strongly predictive of mortality from

cardiovascular disease [107, 108]. In a recent study with shorter follow-ups, on a very large number of patients, the same phenomenon was observed [109]. In this study the observation of the deleterious effects of albuminuria was also, however, based on patients with clinical proteinuria, excluded in previous studies because of their well-known poor outcome. In patients with long-standing diabetes and late microalbuminuria it can be assumed microalbuminuria increases relatively slowly [110]. Therefore these patients perhaps have a somewhat different and more "benign" prognosis than "fast track" patients, diagnosed early on with microalbuminuria or proteinuria. Such interpretations could, however, still be problematic because we are not dealing with two distinct entities but rather have regarded microalbuminuria as a continuous variable.

Microalbuminuria in Type II diabetes

In a follow-up study first communicated in 1983 [111] it was shown that microalbuminuria in Type II diabetes is strongly predictive of an increased mortality risk [112]. This observation has since been confirmed in numerous studies [113]. Other factors could be associated with poor prognosis such as long-term hyperglycaemia and high blood pressure. Microalbuminuria seems though to be the strongest overall predictor of mortality as has also been found in non-diabetic population-based studies [8]. Interestingly, poor metabolic control has recently been shown to predict microalbuminuria [114, 115] and could also be a risk factor for its progression, whereas high blood pressure can be more important later on [114, 116–125]. Poor glycaemic control correlates with typical diabetic glomerular lesions [126]. More so-called "unspecific" lesions can also be observed but non-diabetic microalbuminuric controls are lacking, which is problematic. Indeed there might be some misclassification of patients in such studies because albuminuria usually decreases with antihypertensive treatment [126]. The "unspecific" lesions can also be considered as characteristic lesions in diabetic patients, again making exact classification problematic not necessarily in daily ordinary pathology practice but in scientific work which is to be tested by other investigators. Other studies have shown abnormalities in microalbuminuric Type II diabetic patients [127]. Among the many risk factors analysed [118–124] hyperglycaemia and hypertension seem to be of particular importance, as documented in initial studies on the relevance of higher albumin excretion rates in relation to other risk factors [8–10]. Thus again there is a requirement for two risks; hyperglycaemia and high blood pressure factors must combine to produce important clinical disease [114, 116]. Since microalbuminuria in Type II diabetes is a better predictor of cardiovascular than of microvascular disease other macrovascular disease factors must be taken into consideration. These include hyperlipidaemia whose reduction plays an important part in secondary prevention of cardiovascular disease in Type II diabetes.

The natural history of microalbuminuria in Type II diabetes has been surveyed recently [116]. Short-term intervention treatments are not usually very effective [119, 125]. Long-term glycaemic control as in the Kumamoto study [40] and the UK prospective diabetes study [128–131] have, however, proven rather efficient especially when combined with long-term antihypertensive treatment [130, 131]. Detailed accounts of microalbuminuria in the UK study are still awaited.

Difference between Type I and Type II diabetes

More and more evidence suggests that the course of renal abnormalities is similar in Type I and Type II diabetes. Obviously, there are exceptions because patients with Type II diabetes tend to be elderly and obese. This means hypertension is seen much earlier in Type II diabetes with subsequent renal damage. Another important point is that Type II diabetes can remain undiagnosed for many years and therefore many patients will have renal and retinal as well as cardiovascular damage at the first clinical diagnosis [29]. Risk factors for the development of renal disease include poor metabolic control and high, or increasing, blood pressure for both types. With microalbuminuria again glycaemic control and high blood pressure are important risk factors that can be controlled. In overt renal disease, there is a clear-cut correlation between blood pressure and decline in glomular filtration rate. There is also a correlation in Type I diabetes between glycaemic control and a decline in GFR [87, 88] but this is less clear in Type II diabetes where there seems to be no correlation between rate of decline of GFR and HbA_{1C} [116].

Treatment modalities seem to be the same as confirmed by the UK prospective diabetes study [128–131]. An important point is that many patients with Type II diabetes have cardiovascular and cerebrovascular disease and might suffer premature mortality. Certainly, this can be modulated by early antihypertensive treatment as shown in several trials [132–138] (Table 8) and also by lipid lowering [139].

Microalbuminuria in population-based studies

Microalbumininuria is present in 5–10% of elderly populations [20, 28] and usually relates to hypertension but also to other risk markers of cardiovascular disease, such as abdominal obesity, hypertension and hyperuricaemia. The relation between microalbuminuria and early mortality in population-based stud-

Table 8. Positive effect on cardiovascular end points in Type II diabetes by AHT

	FAVOURS:
1. SHEP [137]	Diuretics vs placebo
2. ABCD [135]	ACE-I vs CCB
3. Facet [132]	ACE-I vs CCB
4. HOT [134]	Strict control (CCB-based)
5. UKPDS [130]	Strict control (ACE-I + β-bl-based)
6. SYST-EUR [133]	CCB vs placebo
7. CAPPP [136]	ACE-I vs conventional

AHT, antihypertensive treatment; CCB, calcium channel blockers; β-bl, beta-blockers

ies was first documented more than 10 years ago [20, 27]. Accordingly microalbuminuria should be included in epidemiological studies with a focus on cardiovascular and metabolic diseases. In essential hypertension, microalbuminuria is often diagnosed and predictive of cardiovascular and also of progressive renal disease [101]. This is relevant to "Syndrome X" where similar observations were made decades ago by Kylin in 1923, Himsworth in the 1930s, Vague in the 1940s, and Avogaro and Crepaldi in 1965 [140–144]. It is, however, still perhaps a too vaguely defined entity [145] which often most strongly relates to simple obesity. In contrast microalbuminuria is more related to high blood pressure and diabetes as shown in the Hoorn Study [30] and should not be included in the "syndrome".

Provocation tests to detect early abnormalities in renal function

It was shown several years ago by Karlefors [146] that exercise induces a clear-cut increase in blood pressure, in particular, in diabetic patients with renal complications and blood pressure values in the upper normal range. We used this concept to describe and detect nascent changes in renal function prior to microalbuminuria and in certain patients quite a pronounced increase in albuminuria occurred during exercise, especially in those with pre-existing microalbuminuria [147–150]. Increases in albuminuria are associated with raised blood pressure during exercise, an association that is quite strong. It is, however, not clear whether this test is predictive of advancing renal disease. Although the idea seems quite attractive, clear-cut, follow-up studies have not been conducted. Therefore, in the clinical situation multiple baseline measurements are preferred to precisely define the degree of early renal involvement. To this end we measure the albumin: creatinine ratio at each visit to the clinic [12]. It has also been proposed that tests that block tubular reabsorption, e.g. by lysine or other dibasic amino-acids be used but again these are too laborious for clinical use [151, 152] although, important physiological information on the nature of renal involvement in diabetes has thereby been obtained. By apparent complete blockade of tubular reabsorption, albumin excretion rises from 5 to approximately 300 μg/min, thus providing an estimate of transglomerular passage of albumin [57, 151]. In addition other provocation tests have been examined [153–157].

24-h Ambulatory blood pressure measurements

Ambulatory blood pressure measurements were first developed in the 1960s by Sokolow's [158] and Pickering's group [159] and in the 1980s by Rubler in diabetic patients [160]. The technique used was initially quite difficult and demanding not only for the patient but also the physician. With the introduction of more user-friendly equipment, such as the SpaceLabs apparatus, it is now common clinical practice to take ambulatory blood pressure measurements in situations where there is uncertainty as to the precise level of blood pressure, both before and during treatment [161–174]. An important confounding issue to be avoided is the situation-induced "white-coat" hypertension which is just as common in diabetic as in non-diabetic patients [175, 176]. This is also extremely important in clinical trials because fewer patients could be required to document treatment effects [162, 177]. More sophisticated questions might be answered by ambulatory blood pressure measurements. These include: 1) the effect of smoking which seems to increase blood pressure in diabetic patients in contrast to the paradoxical reduction in ambulatory blood pressure in non-diabetic patients [178]; 2) the lower blood pressure in healthy women which is now well established but this conceivably protective biological feature is lost in diabetic patients [165]; 3) the significance of a lack of nocturnal blood pressure "dips" in diabetic patients about which there are still some doubts [175]. In people with normoalbuminuria we have not found any major differences between those with and without diabetes and the phenomenon of dipping has been quite variable and not applicable in clinical settings [175]. It has, however, been reported that Type I diabetic patients on intensive insulin therapy to some extent lack nocturnal dipping [179].

It is important to take ambulatory blood pressure when describing the antihypertensive effect of drugs, e.g. angiotensin-converting enzyme inhibitors [162, 175, 178]. Thus, it is sometimes not possible, with the use of clinically based blood pressure, to detect a reduction in blood pressure that can only be unveiled during ambulatory blood pressure recordings. If it were not for these it could be argued that the inhibitors are renoprotective, even without any detectable effect on blood pressure. Thus by taking the ambulatory blood pressure we observed some blood pressure reduction in such patients, even in trials with relatively few patients [177]. Again, this illustrates the danger

of limiting the concept of renoprotection, by excluding the beneficial effect of blood pressure reduction. Multiple blood pressure measurements with the most exact procedures are therefore essential.

Dextran clearance

Dextran clearance was introduced to describe the glomerular permeability to a large range of molecular sizes [180] and the principle was then used in diabetic patients [181, 182]. When we introduced this technique in our laboratory for diabetic patients [2, 72] we saw no change in dextran clearance in patients with either newly diagnosed diabetes or long-standing diabetes when correcting for prevailing glomular filtration rate [72], since these patients are often hyperfiltering. In patients with microalbuminuria, Deckert [183], in contrast to other studies [184, 185], also failed to find any changes. We were, however, able to see changes in patients with advanced clinical proteinuria but only by long-term collection of urine after dextran infusion and use of very high-molecular weight dextran [2]. Thus in patients with advanced proteinuria only small permeability defects could be described, which could be a paradox because these patients were clearly proteinuric or even nephrotic. Possibly the dextran molecule is not suitable for this purpose, perhaps because it uncoils during the glomerular filtration process and charged dextrans possibly aggregate suggesting a falsely low clearance. The introduction of Ficoll – a molecule with more fixed structure – could or could not provide new information on glomerular permeability to large molecules. Still, in the clinical situation, it is much easier and more practical to use endogenous plasma proteins as markers.

Renal and other organ protection

To define risk markers for progressive renal as well as cardiovascular disease is clearly of interest academically but not necessarily of clinical importance as intervention might not always be possible. Theoretically, intervention should certainly be possible considering the two major risk factors, high blood pressure and hyperglycaemia. Renal protection, defined as any measure to prevent progression of renal impairment, could therefore include control of blood pressure and hyperglycaemia, based on observational risk factor studies, as poor glycaemic control is a major risk factor for progression from normo- to microalbuminuria [114, 115, 171]. In patients with microalbuminuria, glycaemic intervention is not, however, always clinically feasible, although highly desirable [15, 186–188]. The background could well be that patients with microalbuminuria previously have had poor metabolic control which could be inherently difficult to treat. In overt nephropathy, poor metabolic control is certainly associated with rapid progression [15, 87, 88]. Therefore during the entire course of renal involvement in diabetes good metabolic control is a main issue, likewise for the prevention of retinopathy, as well as, to some extent, cardiovascular disease, both in Type I and Type II diabetes. Table 7 describes the relation between intermediary end-points and the decline in glomular filtration rate. This is a dramatic development over the last 40 years as it has been argued that hypertension was "essential" to maintain sufficient organ perfusion and survival [35].

Early anti-hypertension treatment to prevent progression in renal disease in microalbuminuric patients

In this context it is important to consider blood pressure as a continuous variable [189]. It cannot be argued that there is a clearly defined level representing high blood pressure unless long-term studies are conducted to observe correlation between blood pressure and development of cardiovascular and renal lesions. This applies to both Type I and Type II diabetes and the general population. Certainly diabetic patients could be more susceptible to renal damage than non-diabetic people or patients with essential hypertension, as related to blood pressure [18, 147].

This was the basis for our early intervention study in which microalbuminuric Type I diabetic patients with so-called "normal" blood pressure were enrolled in a clinical trial with a self-controlled approach [189–191]. In this study it was documented that antihypertensive treatment with beta-blockers could lead to regression of microalbuminuria. Further studies along this line showed that antihypertensive combination treatment in such patients is associated with declining albuminuria and slow progression (no decline in GFR) in early diabetic renal disease [192–194]. At present most diabetic patients are on combination therapy.

The benefit of this new therapy was clearly confirmed using angiotensin-converting enzyme inhibitors in the treatment of patients with microalbuminuria [195]. Numerous studies [196–203] have confirmed the effect of these inhibitors in Type I diabetes leading to regression of microalbuminuria, as also documented in a recent meta-analysis [203]. Interestingly, this effect is also seen in very early renal involvement in diabetes, such as in patients with mild microalbuminuria [177] between 20 and 70 μg per min. In this 2-year controlled clinical trial the progression expected was seen in the untreated control group with a mean increase rate between 15 and 20%. With treatment using ACE-inhibition, there was a clear-cut reduction in albuminuria as seen in

earlier studies in which the subjects had a higher degree of microalbuminuria. Therefore treatment could be effective quite early, just after the development of microalbuminuria as now advocated by recent guidelines [204]. In the study [177], the specific renal impact of ACE-inhibition was clearly documented. A fall in albuminuria correlated with a fall in filtration fraction. The long-term aim is, however, not regression of microalbuminuria per se, although this might be a reliable surrogate marker, but to prevent a decline in GFR. This requires long-term studies over 6–8 years. Indeed Mathiesen and co-workers [197] were able to show that the effect of ACE-inhibition is not always long lasting. Importantly, patients with clinical proteinuria had well-preserved GFR after a pause in treatment but only when ACE-inhibitors had been given over the previous 8 years. Without antihypertensive treatment, there was a clear-cut decline in GFR in those developing proteinuria. This is the first study to document a long-term preservation of GFR in Type I diabetes [197] as seen in Type II diabetes [200, 201].

Renal protection in Type I diabetes with overt nephropathy

There has been some discussion about the definition of renal protection in diabetes and in other renal diseases. In my view, a key point is that renal protection should mean GFR is better preserved by treatment, irrespective of its modality. It has been proposed that "renal protection" should be defined as a kind of treatment that preserves GFR, on top of the effect of blood pressure reduction. In my mind this definition is too narrow. Any kind of treatment that prevents a fall in GFR or reduces fall rates in GFR should be termed reno-protection. A broader and weaker definition would be "reduction in proteinuria" since this nevertheless is often associated with the prevention of decline in GFR [15].

Initially, we studied early renal involvement in diabetes describing the now well-known phenomenon of hyperfiltration [1, 72, 205, 206]. Subsequently it was found pertinent to study the natural course of renal function changes in diabetic patients, especially in those with microalbuminuria and clinical proteinuria [207–210]. It became clear that a rise in blood pressure was associated with a fall per period of time in GFR in proteinuric patients and therefore anti-hypertensive trials were initiated with a self-controlled design. This was essential to gain optimal sensitivity due to the limited number of patients available [211].

It soon became clear that antihypertensive treatment with beta-blockers and diuretics and sometimes vaso dilatators was quite effective in preserving GFR [211–214] and in improving renal prognosis [215, 216]. These seem to be the first studies to document

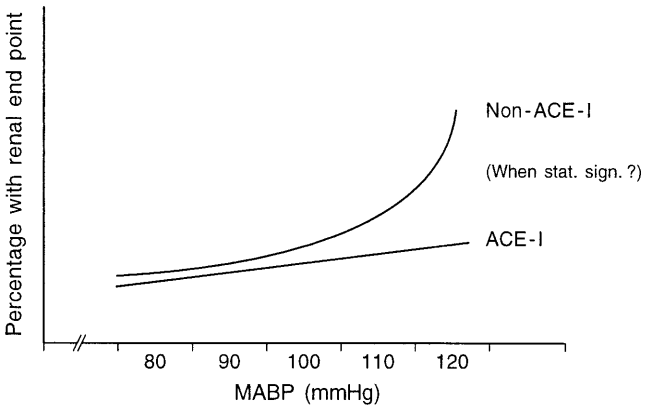

Fig. 2. Nephropathy in Type I diabetes. The concept of renal protection in relation to blood pressure according to E. Lewis [218]. MABP = mean arterial blood pressure. At which level is blood pressure differing significantly?

reno-protection (using the above definition) by antihypertensive treatment in diabetes specifically and in renal disease in general. Later studies were conducted in other centres, in particular in Sweden [217] in patients with overt diabetic renal disease. All results suggested that the fall rate in GFR could be reduced by about 50 per cent from 10 ml · min^{-1} · $year^{-1}$ to 5 ml · min^{-1} · $year^{-1}$ or even more by more effective antihypertensive treatment [15, 214]. To some extent, this effect seems to be independent of the type of antihypertensive treatment and depends rather more on blood pressure reduction per se although there could be some disagreement [15]. The largest study so far conducted in overt renal disease in patients with Type I diabetes was the Collaborative Study in the United States [218]. Again this showed antihypertensive treatment to be effective in Type I diabetes. The study compared the use of ACE-inhibitors with other agents to control blood pressure. With a lower and more satisfactory degree of blood pressure attained during treatment, the effect with ACE-inhibitors and other agents was the same (Lewis, personal communication) as illustrated in Figure 2. In contrast with higher blood pressure the ACE-inhibitors seemed to be more efficient, although a strict cut-off has never been defined [219]. In other studies it was found that the blood pressure level was important for the determination of the rate of decline in GFR and also some effect was observed by HbA_{1C} as seen in other studies [15]. In Weidmann et al.'s meta-analysis [220] on proteinuria as a surrogate marker the effect of ACE-inhibition became progressively less as lowering of blood pressure was more intense [219]. In non-diabetic renal disease ACE-inhibition is also an important treatment strategy [221].

In my mind, it is not productive to exclude, by definition, antihypertensive treatment as a reno-protective measure. I would prefer that all measures which protect against a decline in GFR be included in the

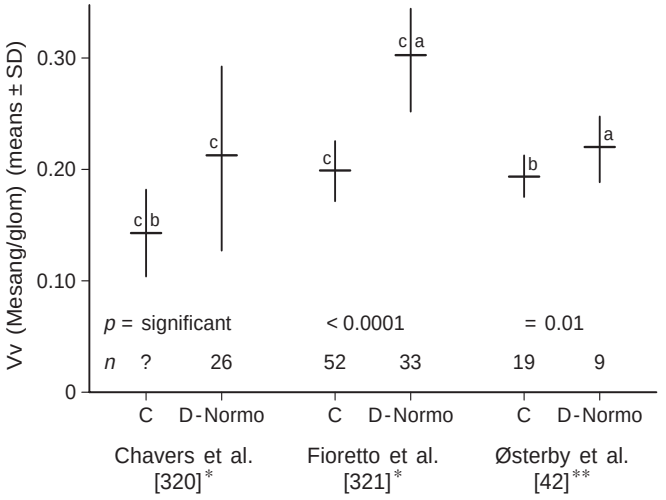

Fig. 3. Type I diabetic patients with normoalbuminuria (D) and non-diabetic renal donors (C). Data from Minneapolis and from Aarhus. a b, of note the large differences between Aarhus and Minneapolis. c Surprisingly big differences between two sets of data from Minneapolis. *Request for pancreas transplant (why?). **Protocol biopsies

definition both in diabetes and in other renal diseases. It is clear that antihypertensive treatment is important, however, in most renal diseases as suggested by our long-term studies in 1982 [211], subsequently confirmed [219], also for cardiovascular disease [130, 131].

Glycaemic control and glycaemic measures

It would seem plausible that diabetic lesions in the kidney and in the eyes, specific for diabetes, are caused by the diabetic state, especially hyperglycaemia. For many years, there was doubt however about this association, mainly because of difficulties in documenting long-term glycaemic control. The large-scale observational study conducted by Pirart and co-workers, however, showed a clear correlation between glycaemic control and the development of microvascular and neurological complications [84]. Intervention studies conducted in Scandinavia and elsewhere supported these observations [15] which were later confirmed by the DCCT as to the development of microvascular and possibly also macrovascular lesions. This formed the basis of the concept of glucotoxicity [41]. Nyberg et al. were the first to observe fairly stable GFR in patients with well-controlled metabolism [222] which was later confirmed [87, 88]. They showed that the decline in the rate of GFR correlated with HbA_{1C} and strong evidence for an earlier effect was obtained in the DCCT [41]. Thereafter, optimal glycaemic control became the elusive golden standard for care in Type I diabetes. Most experts would very much support this view, also for Type II diabetes, when intervention studies related to microvascular disease are positive [40] and there is also a clear correlation between glycaemic control and the development of complications in observational studies [186].

Over the past 25 years, we have observed a radical change in the management of patients, driven by new methods, such as home monitoring of blood glucose, insulin pumps, insulin pens, along with better monitoring of glycaemia, as well as better documentation of complications as measured by retinal photographs and microalbuminuria. Although insulin pumps were introduced around 1980 [223] and stimulated our hope for a practical way to achieve near-normoglycaemia [224–232], for many reasons they are used nowadays by fewer and fewer patients.

Pancreas transplantation, as a more radical approach towards euglycaemia, was proposed even earlier and was also thought to have great promise [233–235]. The idea and its considerable impracticality has been evaluated recently [236]. A new long-term study [237] suggested that the glomerular lesions in diabetic nephropathy could heal not after 5 but after 10 years of normoglycaemia effected by isolated pancreas transplantation. It should be noted that three of the eight patients in fact initially had normoalbuminuria, which in our experience (by strong contrast to the Minneapolis group) is associated with very limited lesions [47] (Fig. 3) and by definition such patients do not have nephropathy [14, 15]. Four patients had microalbuminuria and only one proteinuria, that is only one with overt nephropathy. Only open, nonsclerosed glomeruli were evaluated and no information on change in number of occluded glomeruli is available. Also analysis of interstitial expansion or vascular lesions would have been important considering necessary long-term treatment with Cyclosporin A. Biopsies were not taken from two patients at the follow-up because they had developed end-stage renal disease, so they were hardly normal again from any point of view. The follow-up rate of the very initial total cohort (at year zero) is not recorded. A fall in GFR (from 108 to 74 ml/min) was noted in patients that were followed for 10 years, hardly a sign of regression. It would be important to see this study confirmed but for practical reasons this is not to be expected. The study could have problematic implications if it were to create overoptimistic views on the usefulness of pancreas transplantations. Also it is noteworthy that pancreas transplantation does not always lead to a complete return to normal metabolism [238].

Angiotensin-converting enzyme-inhibitors

Angiotensin-converting enzyme-inhibitors are antihypertensive agents which in several experimental studies [239], and also in human studies in diabetes [195], had a specific effect on renal function reducing

trans-glomerular pressure. Thereby, a reduction in albuminuria has been shown by ACE-inhibitors; likewise, the rate of decline of GFR and even its arrest was seen in patients with microalbuminuria [197]. Therefore, the use of ACE-inhibitors has become a standard initial choice in early and late antihypertensive treatment of diabetic patients, but quite often combination therapy is required, also in clinical trials [196]. It is still debatable whether, with exactly the same effects on blood pressure, differences still remain between ACE-inhibitors and other anti-hypertensive agents though this argument has been resolved for beta-blockers, which exert the same beneficial action as ACE-inhibitors in Type II diabetes [131]. Nevertheless the debate seems to have been largely academic as usually ACE-inhibitors are quite efficient and only have a few side effects (no impact on glycaemia), at least early in the course of renal involvement in diabetes. In any case, the introduction of ACE-inhibitors has been a major step forward in diabetes care. We are still working on a new development combining ACE-inhibitors with diuretics and cardio-selective beta-blockers as a potentially even more efficient treatment [194]. Years ago, it was suggested that antihypertensive treatment could impair renal circulation and thus be deleterious [35]. The small reduction in GFR along with reduced proteinuria is likely to be indicative of a beneficial effect [15]. Based on many studies, we now know that low blood pressure obtained by treatment or spontaneously is protective against the development of more advanced glomerulopathy and decline in GFR [219]. Renal vascular stenosis in diabetic patients very rarely imposes clinical problems [130, 131] and needs usually not to be screened for before treatment [240].

The concept of antihypertensive combination therapy in diabetes

Quite often in clinical practice antihypertensive combination therapy has to be used. This is not surprising considering the complex nature of high blood pressure in diabetes. With particular regard to renal involvement it could be advantageous to use ACE-inhibitors because of their effect on glomerular pressure [36, 239, 241]. Indeed, there could also be an additional effect on growth factors and cytokines by ACE-inhibition. Nevertheless, early on there could also be general hyperfusion related partly to cardiac involvement [242] that could be reduced by the use of beta-blockers. This concept of general vascular hyperfusion in the genesis of vascular complications was proposed by Parving et al. [243]. In many Type I and Type II diabetic patients there are signs of sodium retention and therefore diuretic treatment could be beneficial.

Following these lines we have used a combination of beta-blockers and ACE-inhibitors [192, 193, 194] with diuretics as a basis therapy. This kind of treatment was effective in reducing albuminuria and persistent studies have shown long-term preservation of GFR in patients with early renal disease [194]. Therefore, this concept of treatment could prove important, also in the early management with only limited blood pressure increase. Very few side-effects are seen with early combination therapy where moderate doses can be used. This concept could well prove profoundly renoprotective in long-term studies.

Renal involvement and treatment in patients with Type II diabetes and proteinuria

Patients in this category have a poor prognosis with a rapid decline in GFR, correlated with blood pressure, but not HbA_{1C} [15, 244]. The prognosis is also poor because many patients develop cardiovascular disease which is the most common reason for the observed considerable increase in mortality. Therefore, it is important to conduct new trials in this area, indeed two major trials are in progress using treatment with an angiotensin-converting receptor blockade compared with standard treatment. In one study, treatment with calcium channel blockers is used in one arm. Some controversy has arisen recently regarding calcium channel blockers in diabetes [245, 246]. The results of large new trials are eagerly awaited, in the hope it will be possible to improve the care of these patients. In my mind, however, it is clear that early treatment, including screening of patients with microalbuminuria and well-preserved GFR would still be essential along with early antihypertensive treatment in general and better glycaemic control.

So far treatment with the receptor blocker Losartan has been effective in normoalbuminuric and microalbuminuric essential hypertensive patients [247]. In normoalbuminuric Type I diabetes, Losartan not only reduces blood pressure (in normotensive patients) but also hyperfiltration and insulin resistance and this is of potential benefit in Type II diabetes [248]. The clinical relevance remains though to be established.

The natural history of diabetic renal disease, a sound concept?

The term "the natural history of diabetic renal disease" has been widely used [249] but possibly it is no longer appropriate simply because we have and use many measures to change the course of renal disease in diabetic patients. The natural history can be a term used to describe the normal course in diabetic

patients in purely observational studies. It is however now clear that the course of renal disease strongly relates to glycaemic control and with HbA_{1C} lower than 7.5% microalbuminuria might not develop at all. Also when microalbuminuria is present there could be an effect of improved glycaemic control although this is difficult since control is often hard to achieve in these patients [188]. In overt renal disease several observational studies in Type I diabetes have shown that the rate of decline in renal function is correlated with HbA_{1C} which excludes the term "natural history" and obviously only applies to untreated patients. In the case of normal blood pressure the rate of decline in GFR is actually low and long-term studies have shown that survivors with diabetes of more than 40 years duration quite frequently have lower than normal blood pressure [81].

Cardiovascular and cerebrovascular along with renal end-points

Cardio and also cerebrovascular diseases are major causes of death in both Type I and Type II diabetes, especially when the kidney is affected. Although the concept of controlled clinical or therapeutic trial has evolved over the past 50 years [250–251], only a few large trials have been conducted in diabetes, the first being the UGDP (University Group Diabetes Program) [252] which is now, after the UKPDS [128–129], mainly of historical interest. No real large-scale controlled trials were done when introducing sulphonylureas [253], biguanides or insulin but this has changed now [128–129]. There has therefore been an increasing interest in cerebrovascular and cardiovascular end-points, especially in Type II diabetes with respect to effective modulation, mainly with antihypertensive treatment strategies, which show a beneficial effect (Table 8). Most studies use ACE-inhibitors but it is noteworthy that any reduction in blood pressure seems to be important. Certain trials show ACE-inhibitors to be superior to calcium-blockers and also conventional treatment [132, 135, 136]. Importantly, the UK prospective diabetes study showed a similar outcome using ACE-inhibitors and beta-blockers [128, 129]. Fewer side effects occurred with the use of ACE-inhibitors. This study also clearly showed that careful blood pressure monitoring and effective treatment reduce very considerably cardio and microvascular end-points (around 30%). Therefore, antihypertensive treatment should be given great priority in the management of patients with Type II diabetes. The UK prospective diabetes study showed some effect of optimal glycaemic control but due to the nature of the trial this was not so evident. Combined euglycaemia ($HbA_{1C} \approx 6$–7%) and normotension is, however, highly protective when blood pressure is around 130/80 [79, 80].

Meta-analysis in diabetes

The meta-analysis approach was originally worked out in the physical and mathematical sciences [250, 251] but was soon used in medical studies to combine, for instance, data from trials and from observational cohorts, e.g. on the correlation between hard end-points such as mortality compared with risk factors such as blood pressure. Indeed studies with observations in many subjects have documented a clear linear correlation between hard end-points and blood pressure down to normal values.

Parving et al. did a meta-analysis of many small trials in the evaluation of progression of renal disease in Type I diabetic patients treated with ACE-inhibitors and non-ACE-inhibitors and found very similar progression rates during treatment [15, 214]. The analysis was before the Ed Lewis Study [218]. Most trials with microalbuminuric patients in Type I diabetes are of limited size and therefore it would be valuable to do meta-analysis also on such patients as done by Chaturvedi along with our group and others [203]. The beneficial effects on regression of microalbuminuria were better documented in this meta-analysis than in individual studies of homogeneous Type I diabetic patients.

It is important to consider homogeneity before preceding with any meta-analysis otherwise the situation can be problematic such as in the metformin arm of the UK prospective diabetes study [129] in which a beneficial effect was found in newly diagnosed obese people with diabetes. Later on in other patients with longer standing diabetes, poor glycaemic control and probably more advanced vascular damage, the beneficial effect of combination therapy (metformin plus sulphonylurea) was lost and an adverse effect was even noted. From a clinical point of view these two patient groups are different and in my view it is not relevant and even incorrect to make a meta-analysis in such a situation. There are, however, people who support the Petonian approach and believe that meta-analysis can be important even with non-homogeneity [254]. This has been questioned suggesting that meta-analysis does not always give the correct answer, especially if the question is not correctly formulated and patient material not homogeneous [255–261].

Guidelines with origin in pathophysiological and clinical trials

The World Health Organisation – International Society of Hypertension (WHO-ISH) Liaison Committee on hypertension was established in the mid-1970s and has subsequently produced several guidelines, the first in 1975 [262]. New guidelines have recently appeared [263] also related to hypertension in diabetes.

Table 9. Suggested target blood pressures during antihypertensive treatment. Systolic and diastolic should both be attained e.g. < 140/85 mmHg means less than 140 systolic and less than 85 diastolic

	Clinic BP		ABPM or home BP	
	No diabetes[a]	Diabetes	No diabetes[a]	Diabetes
Titrate to DBP:	≤ 85	≤ 80	≤ 80	≤ 75
Optimal BP:	< 140/85	< 130/80	< 130/80	< 125/75
Suboptimal BP:	≥ 150/90	≥ 140/85	≥ 140/85	≥ 130/80

[a] In those with high cardiovascular risk and initial blood pressure 140–159/90–99 mmHg there could be a case for adopting the targets for diabetic patients (British Hypertension Society 1999).
ABPM, ambulatory blood pressure monitoring

Several of these new guidelines have a similar approach [264–269]. There is a clear emphasis on early and effective antihypertensive treatment in patients with diabetes suggesting a lower threshold for the start of the treatment and also a lower blood pressure goal during treatment. Angiotensin-converting enzyme-inhibitors are often preferred as initial agents but combination therapy is often warranted. In view of the recent observation that different types of drugs (ACE-I, beta-blockers, calcium channel blockers and diuretics) reduce cardiovascular risk in Type II diabetes there are different treatment options. In diabetic renal disease ACE-I is however preferred. We should aim to achieve a blood pressure around 135/85 mmHg during treatment (Table 9).

The British Hypertension Society proposes [266]: (1) "The threshold for antihypertensive treatment in Type I diabetes is ≥ 140/90 mmHg. The target blood pressure is < 130/80 mmHg, or lower (< 125/75 mmHg) when there is proteinuria ≥ 1 g/24 hours" and (2) "trials support treatment of all patients with Type II diabetes and blood pressure ≥ 140/90 mmHg, aiming for a target blood pressure < 130/80 mmHg. Blood pressures ≥ 140/80 mmHg on treatment should be considered sub-optimal" and (3) "Thus there is evidence from outcome trials in hypertensive patients with diabetes for the efficacy and safety of ACE-inhibitors, betablockers, dihydropyridines, and low-dose thiazides. The choice among these drug classes should be made using the criteria set out earlier for non-diabetic patients. Blood pressure control will usually require more than one antihypertensive drug, and about 30 % of hypertensive patients with diabetes need three or more agents in combination" [266]. A similar approach is seen in Table 9.

The problem is that it can be difficult to achieve such blood pressure in patients with proteinuria and overt renal disease and also in others with cardiovascular problems. Therefore, it is strongly advocated that treatment is started early, e.g. with development of microalbuminuria, even in patients with normal blood pressure. It has also been proposed that treatment should be started even before microalbuminuria [210]. Since complications are so closely associated with blood pressure increase (also in the normal range) this could easily be recommended in future guidelines as we now have effective treatment with limited side effects.

Concluding remarks

This review describes observations in a number of areas related to diabetic renal disease and related topics. Over the past 30 years there has been a great change in the management of the patients with long-term diabetes as described by Lundbæk [270], based on the results of physiological and patho-physiological studies followed by clinical trials which have been quickly implemented into clinical practice and incorporated in revised guidelines. Not all ideas have proved successful although they might have provided important insight into the nature of the disease. Some erroneous concepts have, however, led to setbacks slowing down the introduction of effective treatment in patients. These include a few very preliminary studies which suggested complications are predominantly genetically determined and therefore not readily modifiable. Considering complications to be generated primarily by a combination of glycaemic and haemodynamic factors (especially high blood pressure) – only partially genetically determined – makes the treatment option much more attractive to the clinician [271, 272].

The role of low protein diet is not discussed but the potential nephrotoxic effect of dietary proteins was originally explored by Anitschkow and co-workers in St. Petersburg in 1913 [273]. This gave rise subsequently to the cholesterol research since he fed rabbits so they were not only exposed to a high protein but also a high fat diet. The protein contents of the diabetic diet is still discussed [53, 274] but the cholesterol issue in diabetes, later appeared to be even more important [59].

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