

Renal structure and function in type 2 diabetic patients with or without diabetic nephropathy

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1. INTRODUCTION AND AIMS

Regulation of renal haemodynamics is a vital component in the overall control of renal function [1]. The ability of the kidney to maintain constancy of renal function over a wide range of renal perfusion pressures is termed autoregulation [2]. Impaired renal autoregulation leads to enhanced transmission of the systemic blood pressure into the glomerular capillary network. Understanding the pathogenesis of abnormal renal haemodynamic in the diabetic state seems important, because it has been suggested, that abnormal haemodynamics plays a major role in the development and progression of diabetic nephropathy [3-10].

Several studies have evaluated the effect of hyperglycaemia on renal autoregulation in rat models of diabetes mellitus, some of the studies have revealed impaired renal autoregulation [11-14], and others preserved [15] or even enhanced renal autoregulation ability [16]. Only one human study has evaluated the impact of diabetes on renal autoregulation [17]. Parving et al. [17] demonstrated impaired autoregulation of glomerular filtration rate (GFR) in type 1 diabetic patients with diabetic nephropathy. No studies have evaluated the impact of diabetic nephropathy or glycaemic control on renal autoregulation in type 2 diabetic patients. Furthermore no study has evaluated the effect of nondiabetic nephropathies on renal autoregulation. Therefore we studied the GFR autoregulation in these conditions.

Antihypertensive treatment reduces the rate of decline in GFR by inducing a faster initial and slower subsequent decline in GFR, in hypertensive diabetic patients with incipient or overt diabetic nephropathy [18-20]. This biphasic phenomenon may be due to the effect of antihypertensive treatment and/or changes in autoregulation of GFR [21, 22]. The relationship between changes in renal perfusion pressure and renal autoregulation during treatment with different antihypertensive drugs has been studied extensively in nondiabetic animals [23-26], while the information in diabetic animals is limited [15, 27, 28]. Information is completely lacking in humans. Therefore we decided to study the effects of two classes of commonly used antihypertensive drugs, i.e. an angiotensin II receptor antagonist and a dihydropyridine calcium channel blocker, on autoregulation of GFR in hypertensive type 2 diabetic patients without diabetic nephropathy.

Despite an increasing number of albuminuric type 2 diabetic patients with end stage renal disease, information on the natural history of diabetic nephropathy in Caucasian patients with type 2 diabetes is scanty. The underlying causes of albuminuria in type 2 diabetic patients are heterogeneous [29-31]. However, no study has evaluated the prevalence of nondiabetic kidney disease in unselected

albuminuric type 2 diabetic patients without clinical diabetic nephropathy, and only relatively few studies have investigated the relationship between renal structure, causes of albuminuria and course of renal function [31-36] in albuminuric type 2 diabetic patients. Therefore we performed a study of the natural history of renal function in Caucasian albuminuric type 2 diabetic patients with diabetic nephropathy. Furthermore, we performed a renal biopsy study, to evaluate the prevalence of diabetic and nondiabetic nephropathies and the potential role of demographic, clinical and laboratory data in separating these entities in albuminuric type 2 diabetic patients without retinopathy. The structural-functional relationships and the course of GFR in these patients were evaluated separating the patients with diabetic from those with nondiabetic nephropathies. Finally, we studied the differences in the course of GFR in a cohort of unselected albuminuric type 2 diabetic patients with or without diabetic nephropathy.

2. AUTOREGULATION

The phenomenon termed autoregulation is defined as maintenance of almost constant tissue and organ perfusion despite large variations in perfusion pressure (Fig. 1). Autoregulation mechanisms protect the tissue/organ against hyper- and hypoperfusion by changing the myogenic activity of the smooth arteriolar muscle cells. Increased systemic blood pressure (BP) induces a smooth arteriolar muscle cells contraction, which reduce the arteriolar diameter. Decrease in systemic BP induces relaxation of the smooth arteriolar muscle cells, and thus an increase in the arteriolar diameter. Consequently, autoregulation of the myogenic response not only protects the tissue and organ against hyper- and hypoperfusion, but also against enhanced transmission of the systemic BP into the capillary bed. This mechanism has been demonstrated in the brain [37], kidneys [38, 39], retina [40], coronary arteries [41, 42], intestinal system [43], liver [44], muscles [45], skin [45] and adipose tissue [46].

Impairment of autoregulation capacity may narrow the perfusion pressure range for which tissue and organ perfusion remain unchanged. A reduced perfusion pressure range may lead to a higher minimal and a lower maximal perfusion pressure limit for normal autoregulation. When the perfusion pressure is above and below this

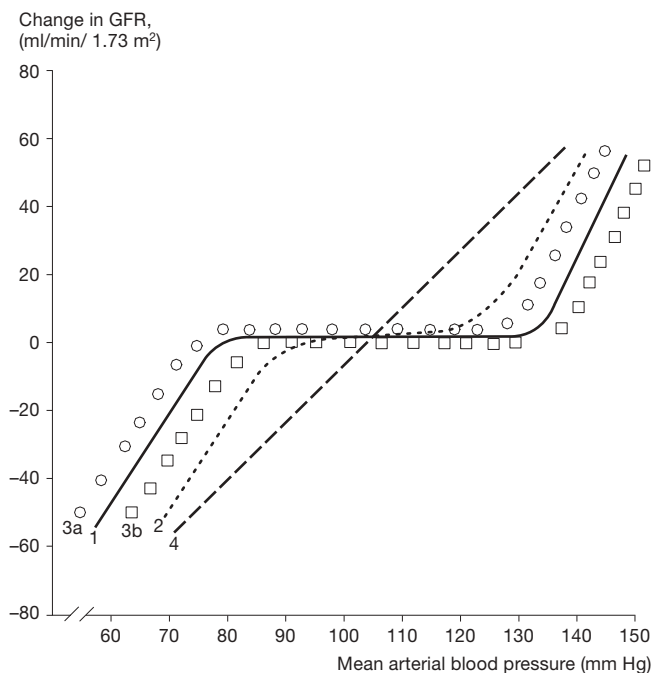


Fig. 1. (1) Normal autoregulation of glomerular filtration rate (GFR), (2) impaired autoregulation of GFR, (3a) shift in GFR autoregulation to the left, (3b) shift in GFR autoregulation to the right, (4) abolished GFR autoregulation.

autoregulation pressure range the tissue and organ may become hyper- and hypoperfused, respectively (Fig. 1). *Alterations in the setting of autoregulation range* may lead to alteration in the upper or lower perfusion pressure limit for normal autoregulation. A decrease in the limits (shift to the left) of autoregulation may cause hyperperfusion and pressure induced damage to the tissue and organ, when systemic BP is high e.g. during exercise. If the limits for autoregulation is increased (shift to the right) the tissue and organ may be susceptible for hypoperfusion and ischaemic injury, when systemic BP is low e.g. during sleep (Fig. 1). *When autoregulation is abolished* the tissue and organ perfusion become totally dependent on the perfusion pressure. This condition may lead to hyper- or hypoperfusion in the tissue and organ, when systemic BP is changing during everyday activity (Fig. 1).

In conclusion, autoregulatory mechanisms are present in most tissues and organs. Autoregulation protect the tissues and organs against systemic hyper- and hypotensive induced damage.

3. AUTOREGULATION OF RENAL FUNCTION

A) DETERMINANTS OF GLOMERULAR FILTRATION RATE

The systemic BP is transmitted through the arcuate arteries to the interlobular artery and reaches the glomerular capillary network through the afferent arteriole (Fig. 2). The glomerular capillary network is connected to the efferent arteriole that leads the pressure into the venous system. The main preglomerular pressure drop occurs during the transmission of the systemic BP from the afferent arteriole into the glomerular capillary network. The large postglomerular pressure drop occurs in the efferent arteriole, which reduce the glomerular capillary hydraulic pressure (P_{GC}) with approximately 70%. P_{GC} remains nearly unchanged between the afferent and efferent arteriole [47].

The structural barrier for glomerular filtration consists of four

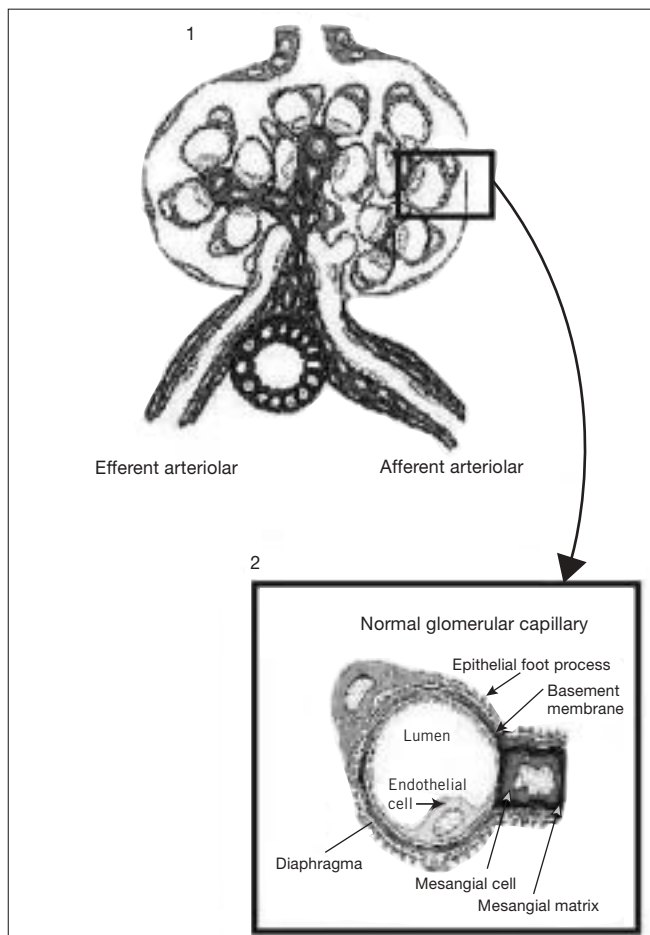


Fig. 2. (1) Normal glomerular structure. (2) Glomerular filtration barrier.

structural components: a thin fenestrated endothelium covering the inner surface of the glomerular capillary, the glomerular basement membrane (GBM), the podocytes with foot processes, which is in connection with the glomerular basement membrane on the outer surface, and finally the pores between the foot processes which are covered with thin diaphragms (Fig. 2). The fluid movement across this structural barrier along the capillary wall at any given point into Bowman space can be expressed as:

$$J_v = k (\Delta P - \Delta \pi)$$

Where J_v is the fluid movement, k the filtration barrier permeability, ΔP and $\Delta \pi$ the transcapillary hydraulic and colloid osmotic pressure gradient between the glomerular capillary and Bowman space, respectively. The fluid protein concentration in the Bowman space in normal and even proteinuric subjects is nearly zero.

The glomerular filtration coefficient (K_f) is the product of k and the surface area for filtration. The total single-nephron glomerular filtration rate (SNGFR) can be expressed as the product of K_f and the net driving force over the filtration barrier (difference between the average transcapillary hydraulic and osmotic pressure differences ($\overline{\Delta P} - \overline{\Delta \pi}$)). The net driving filtration force decline from the preglomerular (afferent) end of the glomerular capillary network and is reaching zero at the postglomerular (efferent) end. This occurs because the ultrafiltration along the glomerular capillary induces an increase in $\Delta \pi$ while ΔP remains relatively constant. An increase in glomerular plasma flow (Q_A) will result in a proportional increase in GFR, when $\Delta P = \Delta \pi$ in the absence of changes in any other determinants of SNGFR, because the axial rate of rise in colloid osmotic pressure in the capillary fluid is reduced. Thus, Q_A is the final determinant of GFR if filtration equilibrium is present.

B) RENAL AUTOREGULATION

Burton-Opitz & Lucas [48] were the first to demonstrate that the most characteristic feature of renal circulation is maintained renal blood flow (RBF) despite extensive variation in systemic BP.

Both human [38] and animal [39] studies evaluating renal autoregulation in pharmacological and surgical denervated kidneys have made it possible to conclude that RBF is determined by an autonomous intrinsic activity of the renal arterioles, which is not dependent upon tonic activity in the sympathetic pathways. The consequence of this statement was that intrinsic mechanisms could respond to extrinsic changes to ensure stability and efficiency of renal haemodynamic control.

The intrinsic autoregulation of renal function is complex and involves several systems, which modulate the vascular smooth muscle tone and diameter of the afferent and efferent arterioles. It is generally accepted that the afferent arteriole is autoregulated by two intrinsic systems: the myogenic [49] and macula densa-mediated tubuloglomerular feedback (TGF) system [50], whereas the importance of the efferent arteriole and other possible mechanisms involved in the autoregulation of renal function is still debated [50]. The setting of the above-mentioned intrinsic systems is believed to be under influence from the sympathetic nervous system [51] and various systemic and local hormones (long-term regulation of GFR) [52].

The myogenic mechanism is based on the ability of arteriolar vessels to alter endogenous tone in response to change in transmural pressure. The phenomenon is well known and was described already in 1902 by Bayliss [53]. TGF is a phenomenon unique to the kidney, by which a change in GFR induce a change in flow and/or pressure [54-56] and/or composition of tubular fluid flowing past the macula densa region of the nephrons [1, 57]. These changes result in alteration in preglomerular resistance and, thus, correct the initial change in GFR.

There are advocates for a singular mechanism mediating autoregulation by the myogenic response [58, 59], whereas others sug-

gest that TGF is the most important mechanism [60]. However, there is emerging consensus that a complicated interplay between both myogenic and TGF mechanisms best explains the efficient autoregulatory response typical of the renal vasculature [50, 54, 61].

Some of the disagreements may reflect significant differences in the degree to which the myogenic and TGF components contribute to autoregulation of RBF among species [62]. Difference in response time to change in perfusion pressure [55] and to location of the two components [63, 64] may also be part of the dispute.

The range of renal autoregulation in animal studies is from 75-95 mm Hg [39, 61, 65, 66] to 180 mm Hg [14, 67] of renal arterial pressure. The range of systemic BP for normal renal autoregulation in healthy humans is partly unknown. But a mean arterial blood pressure (MABP) of 80 mm Hg is usually suggested as the lower limit for normal autoregulation of GFR [62, 68], whereas the lower limit of cerebral blood flow autoregulation in normotensive humans is 50-70 mm Hg, and in patients with severe hypertensive 85-150 mm Hg [69, 70]. Autoregulation of GFR is due to autoregulation of two of the main GFR determinants, i.e. Q_A and P_{GC} [47, 71]. Intrarenal angiotensin II (AII) levels may influence the plateau of renal autoregulation [72-74]. It is therefore possible that range of BP for normal renal autoregulation in patients with diabetes is different from nondiabetic patients, since renin has been suggested to be depressed [75] and AII receptors diminished [76] in patients with diabetes.

We studied the lower part of the GFR autoregulation interval. GFR was measured in all our studies after a single intravenous injection of ^{51}Cr -labeled ethylenediaminetetraacetic by determination of the radioactivity in venous blood samples 180, 200, 220 and 240 minutes after the injection [77, 78]. We used clonidine to induced acute reduction in MABP. Clonidine reduces MABP by a prolonged suppression of the central nervous system sympathetic centres [79, 80]. The decrease in MABP is due to diminished cardiac output not to effects on total peripheral resistance [79, 81]. Clonidine does not alter peripheral sympathetic activity and have no direct pharmacological effects on the renal vessels [79-81]. Intravenous injection of clonidine in normo- and hypertensive subjects induces a slight but insignificant reduction in peripheral and renal vein renin concentration [80, 81].

We defined normal GFR autoregulation as a relative reduction in $\text{GFR} < 13\%$ during clonidine induce acute MABP reduction (the limit of normal GFR autoregulation found in healthy humans [82]), impaired GFR autoregulation as a relative reduction in $\text{GFR} > 13\%$, and abolished GFR autoregulation as relative reduction in $\text{GFR} > 13\%$ accompanied by a clonidine induced relative reduction in MABP less than or equal to the relative reduction in GFR ($\Delta\text{MABP}\% \leq \Delta\text{GFR}\%$).

In conclusion, renal autoregulation is determined by an autonomous intrinsic activity of the renal arterioles. Renal autoregulation is due to a complicated interplay between both myogenic and TGF mechanisms. These systems induces predominantly changes in the afferent arteriole diameter in response to changes in systemic BP. Autoregulation of GFR is due to autoregulation of two of the main GFR determinants, i.e. Q_A and P_{GC} . The range of arterial BP for normal renal autoregulation in healthy humans is partly unknown. Furthermore, it is possible that the range of BP for normal renal autoregulation in patients with diabetes is different from nondiabetic subjects.

C) INTRA- AND EXTRARENAL VASOACTIVE HORMONES AND RENAL AUTOREGULATION

Many vasoactive hormones such as renin, AII, kinins, prostaglandin, thromboxane, endothelial-derived relaxing factor (Nitric oxide or NO), histamin, atrial natriuretic peptide (ANP) and adenosin, have been suggested to modulate renal autoregulation.

Renin. Both the release of renin from the kidney and plasma renin activity remains relatively unchanged within normal GFR autoregulation range [83, 84]. On the contrary reduction in renal artery pres-

sure below the autoregulation threshold induces a marked raise in renin activity [83, 84]. The increased renin activity may lead to an increase in angiotensin I, which is converted to AII by the angiotensin-converting enzyme (ACE). Increased AII levels may cause a contraction primary in the efferent arteriole. Consequently, renin may be important in regulating GFR when BP is near the lower limit of normal GFR autoregulation [85]. The presence of an angiotensin-sensitive efferent resistance component, which is not influenced by the calcium entry dependent vascular contraction, gives additional support to this theory [86]. Furthermore, induced renin inhibition dismissed vascular contractive response when renal perfusion pressure is reduced [87]. However, RBF autoregulation is maintained at a significantly lower BP level than GFR autoregulation, indicating that autoregulation of RBF below the limit of GFR autoregulation involves a dilatation of the efferent arteriole [83].

Angiotensin-converting enzyme. The conversion of angiotensin I to the presser peptide AII and the degradation of the depressor peptide bradykinin to inactive fragments is inhibited during ACE inhibitor (ACEI) treatment [88]. ACEI treatment do not impair renal autoregulation in animals [73, 89-91]. However, ACEI treatment might influence the coupling of RBF and GFR autoregulatory efficiency when perfusion pressure is reduced below the lower limit of normal GFR autoregulation, by inhibiting the increased AII induced contraction of the efferent arteriole [90].

Angiotensin II. The effects of infusion of AII [92, 93] and inhibition of AII (AIIA) [94, 95] on renal autoregulation have been evaluated in isolated kidneys [94] and in situ studies [95], during sodium depletion [85], high salt [74] and normal salt intake [73], during calcium channel blockade [86] and in relation to TGF [72, 91, 96, 97]. The overall conclusions from these studies are, that AII have no influence on overall renal autoregulation within the normal autoregulation range. However, it is possible that AII modify baseline GFR [74] and RBF at low perfusion pressures (high renin) [73, 85]. Furthermore AII may play an important role in setting of TGF activity in the presence of hypertension [72, 97].

Bradykinin. Bradykinin increases RBF [98-101] by dilating both the afferent and efferent arterioles [99], leaving P_{GC} and mean effective filtration pressure unchanged [99]. These changes in renal vascular resistance and RBF do not alter GFR [98, 99, 101]. It is therefore possible that bradykinin modify K_f , however there are disagreements on the impact of bradykinin on K_f between studies [99, 100]. Infusion of bradykinin [101] and treatment with bradykinin analogue antagonist [100] have revealed that bradykinin do not affect autoregulation of RBF and GFR [101].

Prostaglandin and thromboxane. The synthesis of vasoactive prostaglandins and thromboxane is stimulated by bradykinin and AII [102, 103]. Most studies evaluating the effect of prostaglandins on renal autoregulation have used either indomethacin or meclofenamate as prostaglandin synthesis inhibitors in dogs [104, 105] and rats [15, 106-111]. The majority of whole kidney and SNGFR studies show no effect of prostaglandin synthesis inhibitors on autoregulation of GFR and RBF [15, 104, 105, 107]. However, studies evaluating TGF in rats by the stop flow pressure technique [106, 107, 111] have found reduced TGF response to flow changes in the tubulus. Infusion of prostaglandin E_2 increases both tubulus pressure and intrarenal pressure by dilatation of both the afferent and efferent arterioles leaving the effective filtration pressure unchanged [112]. These parallel changes might be the reason for the maintained GFR autoregulation, despite changes in TGF [107]. Even though rat studies have found impaired renal autoregulation of SNGFR [110] during prostaglandin inhibition, it seems that the effect of changes in prostaglandin activation on overall renal autoregulation is limited. Thromboxane the vasoconstrictive component of the prostaglandin system seems to have some influence on TGF [113], however the effect on GFR autoregulation remains to be elucidated.

Endothelium-derived relaxing factor (Nitric oxide). Several hor-

mones, as well as shear stress on the vessel wall influence the release of NO. The effect of NO release is dilatation of the resistance vessels. Shear stress is dependent on perfusion and intravascular pressure. Hence NO is released in response to an increased transmural pressure and may therefore antagonize the myogenic response of vascular smooth muscle cells. The possible impact of NO on renal autoregulation has been evaluated by blockade of NO synthesis via the stereospecific inhibitor *N*^G-nitro-L-arginine methyl ester (L-NAME). Most studies [114-116] show no effect of L-NAME on GFR or RBF autoregulation. However some studies show enhanced TGF [117] and myogenic response to changes in perfusion pressure [118]. The effect of NO on renal autoregulation might be affected by renal damage, since renal autoregulation has been found to be impaired in old hypertensive rats during treatment with L-NAME [119], however no change in renal autoregulation was found during treatment with L-NAME in renal mass reduction models [120]. In rat model of diabetes the response to graded reduction in renal perfusion pressure is similar to nondiabetic rats between 100 and 130 mm Hg [121, 122]. However, when renal perfusion pressure is reduced to the lower limit of normal renal autoregulation, the increased endogenous NO activity in diabetic rat may play a role, since RBF is kept at a significant higher level in diabetic rats compared to the nondiabetic animals [121]. Furthermore, if diabetic rats are treated with L-NAME the differences between diabetic and nondiabetic rats responses to changes in renal perfusion pressure are eliminated [121].

Histamines. Vasodilator histamines effect on renal autoregulation has been evaluated by blockade of the H₁ and H₂ receptor [105, 123, 124]. H₂ receptor blockade has no effect on renal autoregulation [105, 123], while the effect of H₁ receptor blockade on renal autoregulation is still debated [123, 124].

Atrial natriuretic peptide. ANP is a potent vasoactive and natriuretic peptide, which is capable of reducing systemic BP, renin-aldosterone activity, urine osmolarity and increasing RBF, GFR, diuresis and natriuresis [125]. An ANP dose dependent changes in RBF and GFR [126] is combined with a dose dependent dilatation of the afferent arteriole and probably a constriction of efferent arteriole [127-129]. Even though ANP causes vasodilatation of the afferent arteriole, it does not affect the pressure induced vasoconstriction/dilatation of these vessels [128, 130]. These results confirmed previously studies demonstrating that infusion of ANP has no effect on GFR and RBF autoregulation [126]. However rats studies using the stop flow pressure model have shown that TGF is reduced during ANP infusion [131, 132]. But autoregulation of RBF is maintained in rats despite a reduced TGF response during ANP infusion [133]. It is therefore possible, that in vivo experiments might overestimate the impact of ANP on TGF.

Adenosine. Adenosine has been proposed to be the link between changes in renal perfusion pressure and TGF mechanisms through a metabolic pathway. The hypothesis is that increased systemic BP raises RBF and GFR, which thereby increases filtered sodium load and enhances tubular sodium reabsorption via glomerulo-tubular balance mechanisms. The increased sodium reabsorption elevate renal oxygen consumption and energy utilization, thereby increasing ATP hydrolysis and adenosine production. Increased renal tissue levels of adenosine would then preferentially constrict the afferent arteriole, and RBF and GFR would return to the control level [134]. Even though this theory is logic and adenosine might be involved in TGF mechanisms [135], studies evaluating autoregulation of GFR and RBF during changes in renal perfusion pressure in animals treated with continuous infusion of adenosine or with intrarenal inhibition of the adenosine receptor show no impact of adenosine on renal autoregulation [136, 137]. Furthermore, studies have recently showed that ATP through the P₂ purinoceptors might be the mediator of renal autoregulation [138, 139]. The exact mechanisms are not known, but it has been shown that flow-induced shear stress on vessels walls stimulates ATP release from endothelial cells [140].

In conclusion, most studies evaluating the impact of vasoactive hormones on renal function show no effect on overall renal autoregulation within the normal autoregulation range. Vasoactive hormones might have long-term regulatory effect on renal function and thereby induce changes in renal autoregulation range. Furthermore some vasoactive hormones e.g. bradykinin and NO may protect the kidney against hypoperfusion when arterial BP is reduced below the lower limit of GFR autoregulation. The exact mechanisms for renal autoregulation are not known, but ATP might be regarded as an important signal substance.

D) EFFECT OF HYPERTENSION AND AGE ON RENAL AUTOREGULATION

The effect of hypertension and age on renal structure and autoregulation has been studied in different animal models. In *spontaneous hypertensive* rats the setting of the renal autoregulation range is changed to a higher lower blood pressure level [141-143], which is increased further with increasing age [144] (shift to the right, Fig. 1). These changes might reflect an enhanced activity of the calcium channels [145, 146] with exaggerated pressure induced myogenic constriction [147]. Furthermore an age related increase in TGF sensitivity has been revealed [148]. Short-term studies have revealed prearteriolar renal vasculature wall thickening [149], it is therefore probably a combination of intrinsic changes and structural adaptations that causes the change in autoregulation range [150], but the impact of structural vascular adaptation on renal autoregulation is still debated [151, 152]. Morphometric studies have revealed increased renal vascular resistance and diminished renal afferent diameter especially in old spontaneous hypertensive rats [149, 150, 153]. Consequently, the P_{GC} is maintained normal in face of an elevated pressure in these rats. The result is in agreement with histological examinations, revealing that nephrons in spontaneous hypertensive rat kidneys remain intact [154, 155]. Furthermore, in chronic hypertension a shift in cerebral blood flow autoregulation range toward higher lower and higher upper pressure limit is induced. The shift re-adapts towards normal autoregulation range during chronic antihypertensive treatment [156]. These results suggest widespread vascular adaptation during chronic hypertension. The effect of age on cerebral blood flow autoregulation during moderate pressure changes is probably present in the majority of healthy elderly people, but a study focusing on this has not been published [157].

In conclusion, animal studies have demonstrated an adaptive change in the setting of autoregulation range to higher BP limit during hypertension and increasing age (shift of the autoregulation range to the right (Fig. 1)). Human studies are needed to evaluate the possible effect of age and hypertension on the renal autoregulation range in humans.

E) ANIMAL STUDIES OF RENAL AUTOREGULATION IN DIABETES MELLITUS

In experimental diabetes, high blood glucose causes high P_{GC}, RBF and GFR [4]. These findings implies that hyperglycaemia affects regulation of renal function, which have been confirmed in most studies in humans [158-161]. Several studies in streptozotocin diabetic rats and dogs have suggested that hyperglycaemia induces impaired autoregulation of RBF and GFR [11, 14, 121, 162]. Changes in vasoactive hormone activities have been suggested to contribute to impaired renal autoregulation [163, 164]. Furthermore, a rise in growth hormones in diabetic patients induces glomerular structural changes, which may change the regulation of GFR [165]. Diabetic autoregulation impairment develops over time [11, 121], but impaired afferent arteriolar contraction during increased renal arterial pressure can occur in the early course of experimental diabetes [13, 14]. Furthermore diabetes has been shown to impair TGF response [162, 166]. Other investigators have however shown preserved [15] or even enhanced autoregulatory ability (shift of the autoregulation

range to the left) in rats with short time diabetes [16]. Differences between studies may relate to differences between rat models of diabetes. In subtotal pancreatectomy islet mass is markedly reduced, while streptozotocin induced diabetes islet cells are spared but a specific β -cell destruction is induced. These two methods of diabetes resulted in different renal haemodynamic outcomes [16].

In conclusion, even though most animal studies of diabetes, indicate that diabetes per se impair renal autoregulation, it is possible that differences between the diabetic models may have substantially impact on the results. Furthermore no exact mechanisms causing impairment in renal autoregulation in diabetes have been revealed, but changes in vasoactive and growth hormones have been proposed.

F) RENAL AUTOREGULATION IN PATIENTS WITH DIABETES

In the first human study of renal autoregulation Parving et al. [17] studied type 1 diabetic patients with and without diabetic nephropathy. They found no significant change in GFR during acute lowering of BP with clonidine in patients without clinical signs of microangiopathy. The patients had mean blood glucose less than 13 mmol/l during the investigation [17]. In our first autoregulation study [167], we included type 2 diabetic patients with and without diabetic nephropathy. We found no significant change in GFR during acute lowering of BP in normoalbuminuric type 2 diabetic patients. Mean blood glucose was less than 10 mmol/l during the investigation. The above-mentioned studies were not designed to evaluate the potential effect of acute changes in blood glucose on autoregulation of GFR. We therefore performed a randomised crossover study of GFR autoregulation, in normoalbuminuric type 2 diabetic patients during blood glucose <10 mmol/l ("normoglycaemia") and during acute blood glucose >15 mmol/l (hyperglycaemia) [168]. Two out of the fourteen included patients had simple retinopathy, while the remaining 12 had no clinical signs of microangiopathy. Acute reduction in systemic BP induced a mean (SE) reduction in GFR from 92 (3.1) to 86 (3.7) ml/min/1.73 m² during "normoglycaemia" ($p < 0.05$), whereas the reduction in GFR during hyperglycaemia was from 102 (4.1) to 98 (4.2) ml/min/1.73 m², NS (Fig. 3). Mean difference between the mean reductions in GFR during the two examinations was 2.3 (95% CI, -1.3 to 5.9) ml/min/1.73 m², NS. The significant reduction in GFR during "normoglycaemia" might be explained by a more profound reduction in MABP compared to the examination during hyperglycaemia (mean difference 3.9 (95% CI, -0.005 to 7.8)), $p = 0.053$. Furthermore 4 patients had a reduction in MABP below the lower limit of the autoregulation curve (80 mm Hg) during "normoglycaemia", while this did not occur during the hyperglycaemic evaluation. Finally, it is possible that hyperglycaemia enhances renal autoregulation (shift the autoregulation range to the left (Fig. 1)) as described by Mauer et al. [16].

In conclusion, it is impossible to reach a definitive conclusion on the effect of diabetes on GFR autoregulation. The present results suggests that hyperglycaemia has little influence on GFR autoregulation and that diabetes per se do not impair autoregulation of GFR in humans when systemic BP is reduced.

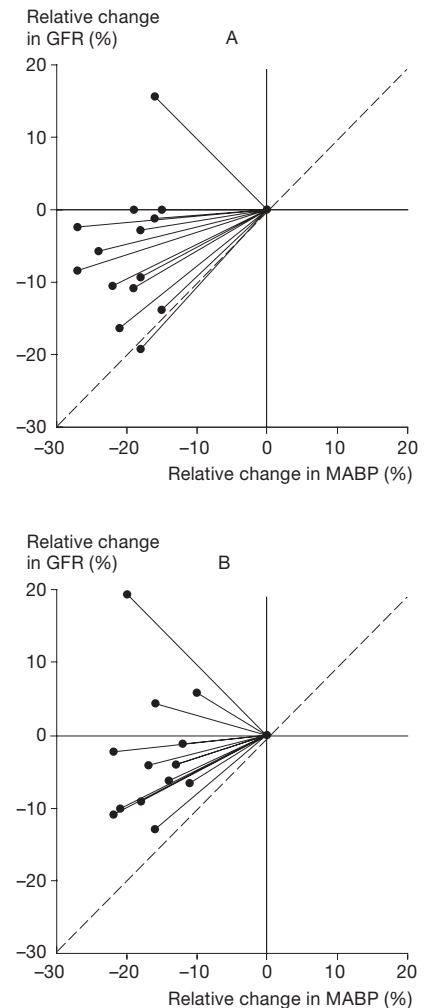
Further studies are needed to estimate the effect of diabetes on renal autoregulation, when systemic BP is acutely increased.

G) RENAL AUTOREGULATION IN PATIENTS WITH AND WITHOUT DIABETIC NEPHROPATHY

Even though animal studies have demonstrated impaired renal autoregulation in models of glomerulosclerosis [169], glomerulonephritis [170], nephrosclerosis [171, 172] and nephrosis [173, 174], only one human study has evaluated autoregulation in patients with kidney disease. In this study Parving et al. [17] demonstrated a wide variation in response to clonidine induced acute BP reduction ranging from normal to severely impaired GFR autoregulation in long-term type 1 diabetic patients with nephropathy. A similar clonidine induced reduction in MABP had no impact on autoregulation in short-term normoalbuminuric type 1 diabetic pa-

Fig. 3. A and B. Relative change in GFR (percentage change of control GFR) and relative change in MABP (percentage change of control MABP) induced by intravenous injection of clonidine.

A. During blood glucose <10 mmol/l.
B. During blood glucose >15 mmol/l.



tients and in the nondiabetic control group. To explore this further, we performed a randomised single blinded case-control study comparing the effect of acute lowering of BP on GFR autoregulation in 26 hypertensive type 2 diabetic patients with (n=14) and without (n=12) diabetic nephropathy [167]. The two groups were matched with respect to demographic data, baseline GFR and BP. Most of the patients in the control group without nephropathy had retinopathy (n=8). Our results demonstrated impaired to abolished autoregulation in hypertensive type 2 diabetic patient with nephropathy, whereas hypertensive type 2 patients without nephropathy only showed moderate signs of altered renal autoregulation, and none of these patients had abolished autoregulation (Fig. 4). We found a significant correlation between the relative changes in MABP and GFR and a significant reduction of fractional renal clearance of albumin in patients with nephropathy. These results suggest that type 2 diabetic patients with nephropathy frequently have enhanced transmission of systemic BP into the capillary network, whereas the glomerular arterioles in type 2 diabetic patients without nephropathy respond adequately to changes in systemic BP. Later we demonstrated in a similarly designed study that patients with nondiabetic nephropathies, as patients with diabetic nephropathy, frequently suffer from impaired autoregulation of GFR [82]. In comparison, an age, sex, BP and baseline GFR matched group of healthy control subjects had preserved autoregulation (Fig. 5). The main results from the above mentioned studies are shown in Fig. 6.

In conclusion, both animal and human studies have revealed impaired renal autoregulation, if nephron number is reduced and clinical signs of nephropathy are present, irrespectively of the underlying cause of the albuminuria. Information on the impact of nephropathy in humans on the upper part of the GFR autoregulation curve is still lacking.

Fig. 4. A and B. Relative change in GFR (percentage change of control GFR) and relative change in MABP (percentage change of control MABP) induced by intravenous injection of clonidine. A. Type 2 diabetic patients with nephropathy. Mean response (○). B. Type 2 diabetic patients with normoalbuminuria. Mean response (○).

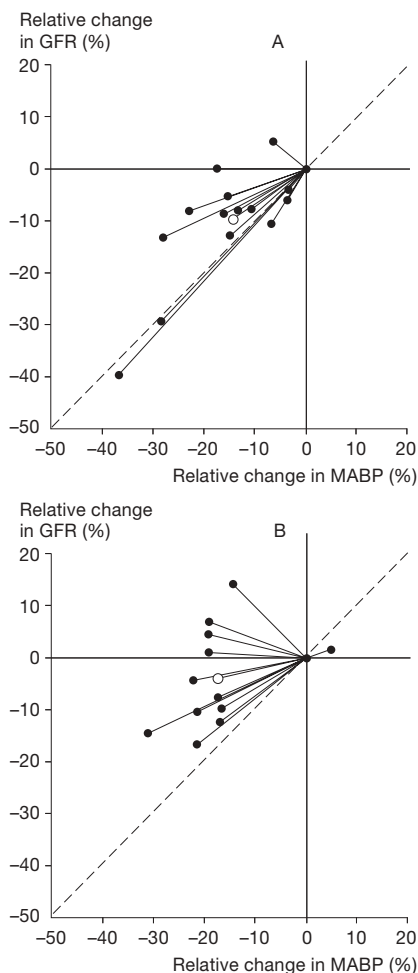
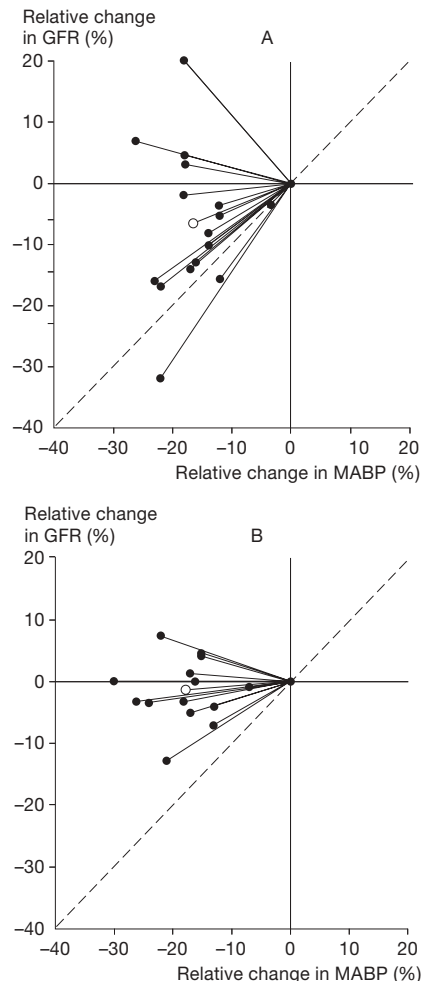


Fig. 5. A and B. Relative change in GFR (percentage change of control GFR) and relative change in MABP (percentage change of control MABP) induced by intravenous injection of clonidine. A. Patients with non-diabetic nephropathies. Mean response (○). B. Controls. Mean response (○).



H) AUTOREGULATION IN EXTRARENAL TISSUES AND ORGANS IN DIABETIC PATIENTS

Diabetic microangiopathy is widespread and causes vascular damage in both arterioles and capillaries [175-177]. The diabetes-induced microangiopathy might change the arteriolar smooth muscle cell response to changes in perfusion pressure, and thereby impaired autoregulation in many tissue and organs of patients with diabetes.

In the brain of type 1 diabetic patients with microvascular complications, a wide variation in response to alteration of BP ranging from normal to severely impaired autoregulation of cerebral blood flow have been demonstrated [178]. In type 2 diabetic patients with retinal microangiopathy of varying severity, the severity of the retinal microangiopathy reflects the cerebral microangiopathy and the cerebrovascular reactivity to changes in perfusion pressure [179]. The reflection of the severity of retinopathy on cerebrovascular reactivity corresponds well to the fact that the retina is an outlying part of the brain. Furthermore a reduced reactivity (vasodilatation) of the cerebral vessels to an increase in arterial CO₂ concentration in patients with type 1 and type 2 diabetes gives further support for impairment of cerebral blood flow in patients with diabetes [180].

Originally, Rassam et al. [181] demonstrated impaired autoregulation of retinal blood flow during acute hyperglycaemia in type 1 diabetic patients with early background non-proliferative diabetic retinopathy. The degree of glycaemic changes in their and our study was similar [168]. The difference in outcome between the two studies might well reflect differences in the mechanisms of retina and GFR autoregulation. An additional reason for the apparent discrepancy between our and their study could be that Rassam et al. [181] studied the upper part of the autoregulation curve by increasing the BP, whereas we, as most animal studies [11, 121, 162], investigated the lower part of the autoregulation curve by decreasing BP. Furthermore, differences in severity of diabetic microangiopathy could

influence the results. Finally, the differences might be related to the vasoactive response to different levels of blood glucose during different changes in BP levels. Hyperglycaemia induces vasodilatation, which can act against the vasoconstrictive response to elevated systemic BP. Consequently hyperglycaemia may impair the function in the upper part of the autoregulation curve. The opposite result may be expected in the lower part of the autoregulation curve. Since lowering of systemic BP induces vasodilatation, which can act together with the vasodilatation induced by hyperglycaemia, and thereby improve the autoregulation capability when BP is lowered (shift to the left of the autoregulation range (Fig. 1)).

Recently studies including both type 1 and type 2 diabetic patients with and without retinopathy has confirmed that retinal autoregulation in diabetic patients is impaired [182, 183]. However these studies, as in kidneys, showed no effect of acute changes in blood glucose [182] and no effect of long-term glycaemic control on retinal autoregulation during increase in systemic BP [183].

In type 1 diabetic patients with clinical microangiopathy the autoregulatory response to both decreased [45] and increased BP [184] is impaired in cutaneous tissue and skeletal muscles. In these patients the autoregulation impairment is independent of level of glycaemic control [185]. In contrast short-term type 1 diabetic patients without clinical microangiopathy have intact cutaneous autoregulation [184]. These results are in accordance with our results in type 2 diabetic patients with [167] and without clinical microangiopathy (diabetic nephropathy or retinopathy) [168]. Diabetic microangiopathy is characterised by an increased arteriolar hyalinosis. This has been suggested to be the main determinant of changes in vascular resistance in the skin [186].

In conclusion, diabetic microangiopathy induce autoregulatory impairment in many tissue and organs. The severity of the microangiopathy seems to be associated with the degree of autoregulatory

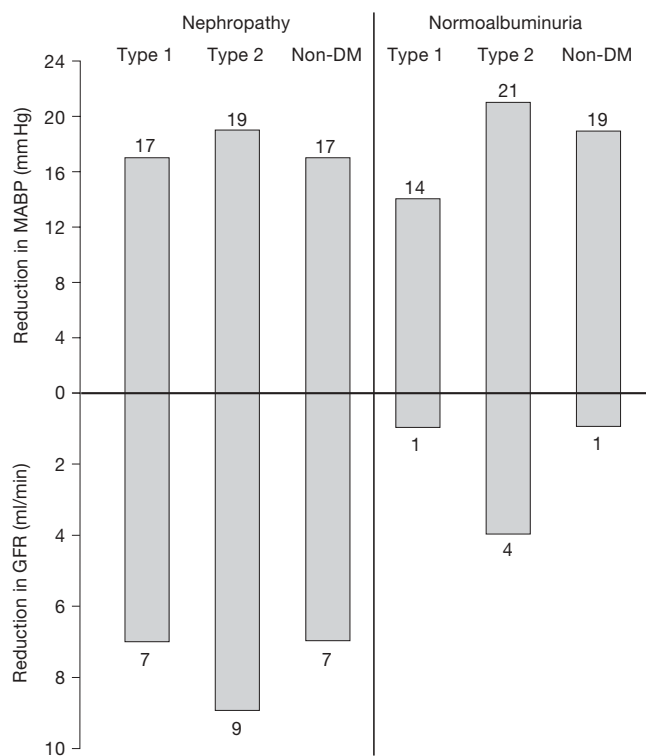


Fig. 6. Absolute reduction in mean arterial blood pressure (MABP) and glomerular filtration rate (GFR) induced by intravenous injection of clonidine in type 1 and type 2 diabetic patients with or without nephropathy, and in nondiabetic (Non-DM) subjects with or without nephropathy.

impairment. The autoregulation impairment appears not to be influenced by short or long-term changes in the blood glucose level when clinical microangiopathy is present. More studies are needed to determine the effect of glycaemic control on renal autoregulation in diabetic patients without microangiopathy.

I) ANTIHYPERTENSIVE TREATMENT AND RENAL AUTOREGULATION

Changes in cytosolic Ca^{2+} is recognized as a pivotal step in mediating smooth muscle contraction. Increase in cytosolic Ca^{2+} can be achieved through influx of the ion from the extracellular compartment, mobilization of intracellular Ca^{2+} from sequestered storage sites, and/or reduced activity of the transport processes involved in Ca^{2+} sequestration or extrusion. The influx of the ion is primarily regulated by mechanisms, which alter membrane Ca^{2+} permeability through influences on specific ion channels. Myogenic control of renal autoregulation is primarily regulated by afferent arteriolar smooth muscle permeability to Ca^{2+} [187, 188], while mobilization of intracellular Ca^{2+} appears to be of minor importance [189]. In accordance, data have revealed that the major vasoconstrictive effect of raised extracellular ionised Ca^{2+} is a pressure dependent alteration in membrane Ca^{2+} permeability [190]. The efferent arteriole seems to be less responsive to changes in membrane Ca^{2+} permeability [188, 191], and respond to AII with a major component of intracellular calcium release. The different calcium signalling mechanisms in afferent and efferent arterioles indicate that the overall autoregulatory response to pressure changes is characterized by a combination of calcium entry and mobilization pathways [192].

Since calcium channel blockers (CCB's) interfere with the influx of Ca^{2+} they may affect normal renal autoregulation. Studies of dogs [86, 193], isolated perfused rat kidneys [190, 194], normal rat kidneys [195], hydronephrotic rat kidneys [130, 196], remnant rat models [197], models of spontaneously hypertensive rats [26, 198-200] and rat models of diabetes [15] have all shown that CCB's impair renal autoregulation. The effect of CCB's on autoregulation seems to be a dose-dependent inhibition of the vasoconstriction

[130, 201], which at high doses make the system pressure-passive (abolish autoregulation) [86] and not influenced by renin secretion [194]. Even though most studies show that both dihydropyridine and non-dihydropyridine CCB's impair autoregulation, some studies indicate that there might be differences within and between the classes of drugs [202, 203]. The different actions of the various calcium channel blockers on renal autoregulation may be related to differences in tissue selectivity and binding sites [25].

Despite the overwhelming evidence suggesting adverse effect of CCB's on renal autoregulation, no study has previously evaluated the effect of CCB's on renal autoregulation in humans. We therefore performed a double-blind randomised cross over study in hypertensive type 2 diabetic patients without overt nephropathy. We selected hypertensive type 2 diabetic patients with normal GFR without overt nephropathy, in order to have a group in need of antihypertensive treatment with normal or only slightly impaired autoregulation. In order to minimise the effect of the patients usual treatment, all antihypertensive treatment was stopped at least 14 days before randomisation. Sixteen patients were treated with the dihydropyridine CCB isradipine retard 5 mg o.d. or matched placebo [204]. Our study revealed that isradipine therapy induced a variable response ranging from no impact to impaired (relative reduction in $GFR > 13\%$) or abolished ($\Delta MABP\% \leq \Delta GFR\%$) GFR autoregulation (Fig. 7). Despite intravenous injection of clonidine more profoundly reduced MABP during placebo treatment as compared to isradipine therapy, none of the patients had abnormal autoregulation during placebo treatment, whereas 38% of the patients showed complete pressure passive vasculature during isradipine treatment. The patients with abolished autoregulation of GFR had an increase in GFR during isradipine treatment. The enhanced GFR probably reflects a more pronounced vasodilatation of the afferent arteriole during isradipine treatment as compared to patients without this response. The isradipine induced vasodilatation enhances the transmission of the systemic BP into the glomerular capillary network resulting in increased P_{GC} and GFR. A reduced autoregulation capacity during isradipine treatment is also supported by the clonidine induced pressure dependent reduction in urinary albumin excretion rate (UAE). In addition to the effect on the kidney, some CCB's are cerebral vasodilators and have the potential for paralysing cerebral autoregulation, whereas ACEI has been shown to improve cerebral autoregulation during hypotension [205]. Consequently, antihypertensive treatment with blockade of the renin-angiotensin system may be superior to CCB's from both a renal and a cerebral autoregulatory point of view.

As described previously, animal studies have revealed that AIIA do not change whole kidney autoregulation. To explore the effect of AIIA on renal autoregulation in humans, we studied seventeen hypertensive type 2 diabetic patients without overt nephropathy during treatment with candesartan cilexetil 16 mg o.d. or matching placebo [206]. We used the same design as described above. Intravenous injection of clonidine induced an equal and significant reduction in MABP during both the placebo and candesartan treatment. The mean difference in changes of GFR between placebo and candesartan treatment were not significant. Furthermore, no significant correlation between the relative changes in MABP (%) and the relative changes in GFR (%) during the two treatments were revealed (Fig. 8). These results are in agreement with the results obtained from animal studies. In our study candesartan furthermore reduced BP without changing baseline GFR. In addition AIIA has been shown not to influence baseline cerebral blood flow, but a shift in the autoregulation curve to the left similar to that of ACEI has been demonstrated. This effect might be due to release of AII-dependent tone in the larger cerebral resistance vessels [207].

In animal studies the effect of Alpha 1-receptor blockade on renal autoregulation have been investigated in normotensive and spontaneously hypertensive rats during stepwise reduction of arterial perfusion pressure [26], in micro-puncture studies [208, 209] and

Fig. 7. A and B. Relative change in GFR (percentage change of control GFR) and relative change in MABP (percentage change of control MABP) induced by intravenous injection of clonidine. A. Treatment with placebo. B. Treatment with isradipine retard 5 mg o.d.

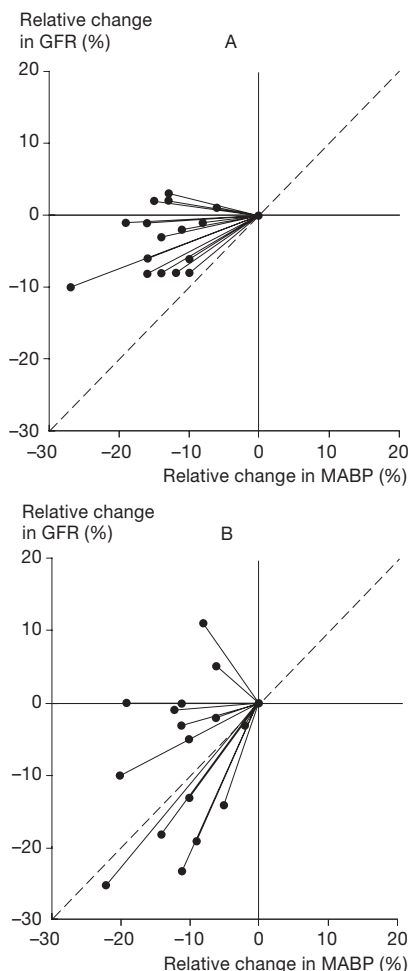
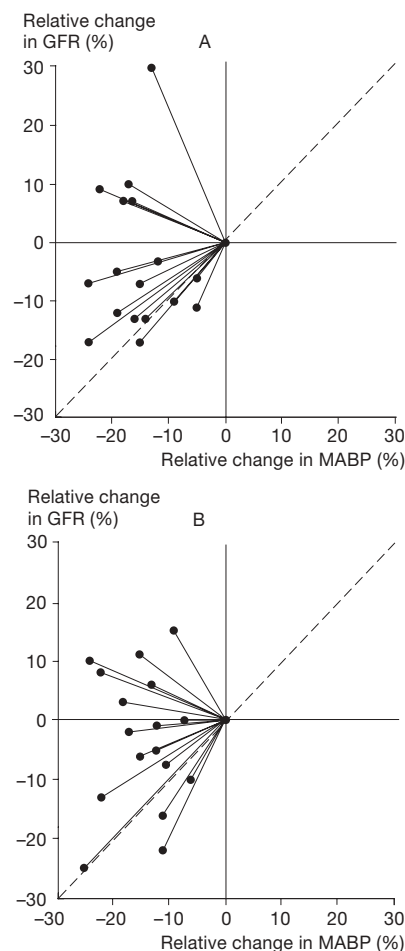


Fig. 8. A and B. Relative change in GFR (percentage change of control GFR) and relative change in MABP (percentage change of control MABP) induced by intravenous injection of clonidine. A. Treatment with placebo. B. Treatment with candesartan 16 mg o.d.



by stop-flow measurements [26, 210]. In the studies Alpha 1-receptor blockade increased blood flow [26], and dilate both the afferent and efferent arteriolar [208, 209]. However, no impact on whole kidney autoregulation has been demonstrated [26, 209].

Only one study has investigated the effect of beta-adrenergic blockade on renal autoregulation. In this study Anderson et al. [94] investigated the effect of propranolol on renal autoregulation during stepwise reduction of renal arterial pressure in dogs. Their results suggested that autoregulation of both GFR and RBF are maintained during propranolol-treatment. Both combinations of alpha 1 and beta-receptor blockade treatment and individual treatment with either of the two have shown a tendency to normalise the autoregulation range of cerebral blood flow in animals [211] and patients with hypertension [205, 212]. Furthermore beta-receptor blockade treatment does not affect cerebral autoregulation in healthy humans [213].

Thiazide diuretics decrease systemic vascular resistance, whereas the opposite effect has been demonstrated in the renal vasculature [214]. This results in a decrease in RBF and GFR [214, 215]. The effect of thiazide diuretics on the afferent and efferent arterioles seems not to be a direct constrictive effect, but rather to changes induced in TGF by the inhibition of sodium reabsorption [214, 215]. However there are disagreements on the effect of thiazide diuretics on TGF [216].

In contrast to loop diuretics, which affect ion reabsorption in the proximal tubules, amilorid mainly affect the sodium absorption connected to potassium and hydrogen secretion in the collection tubules. The different sites of action between these drugs might explain the different effect on renal autoregulation [217]. Whereas amilorid has no effect on TGF, the acute effects of loop diuretics have been shown to be a dose dependent impairment of both TGF [218] and the myogenic response to changes in renal perfusion pres-

sure [61, 219]. However, if loop diuretic is given as a continuous infusion both autoregulation of RBF and GFR are maintained [220, 221].

In conclusion, animal and human studies reveals great differences between different antihypertensive drugs effect on renal autoregulation. Our studies in type 2 diabetic patients suggest that treatment with dihydropyridine CCB's impair/abolish renal autoregulation, while AIIAs have little or no effect on whole kidney autoregulation. Thiazide diuretic impairs renal autoregulation, whereas ACEI, beta-blockers, alpha-blockers, amilorid and long-term loop diuretic treatment have no impact on renal autoregulation in animals. Studies have not yet evaluated the effect of treatment with alpha-blockers, beta-blockers or diuretics on renal autoregulation in humans. Consequently there is a need for further studies of renal autoregulation in humans, to evaluate renal autoregulation during different antihypertensive treatments and to evaluate differences between and within different patient groups.

J) CONSEQUENCES OF IMPAIRED RENAL AUTOREGULATION

The interplay between impaired renal autoregulation on one hand, and systemic BP [222-227], glomerular mechanical strain [8, 228-233], different growth hormones [234-237], glomerular permselective properties [238, 239], diabetes [3, 17, 240, 241], albuminuria [169, 171, 174] on the other hand, and the development/progression of renal histological changes has been studied [173, 222, 242]. Although the pathogenesis in the different models differs in several aspects, impairment of renal autoregulation might induce the following pathological events: Enhanced transmission of systemic BP into the capillary network, induces wide swings and increased glomerular volume [230, 243]. These alterations are further magnified by hypertension [230]. The pressure induced wide swings induces ca-

pillary distension and mesangial stretch [244]. Capillary distension induces glomerular epithelial cell hypertrophy with epithelial cell protein droplets, increase in lysosomes, vacuolisation [245], focal and segmental detachment of endothelial and epithelial cells from the basement membrane [174, 239], segmental capillary collapse with adhesion to Bowman's capsule [245] and fusion of foot processes [242, 243]. These changes combined with increased in P_{GC} [174, 238] lead to changes in size- and charge-selective properties of the glomerular capillaries, and results in increase UAE [174, 239].

Cultured mesangial cells undergoing cyclic stretching demonstrates increased synthesis of protein, total collagen and key components of extracellular matrix (collagen, laminin, fibronectin) [231], this synthesis is further increased in the presence of high glucose concentration [228]. Consequently it is highly likely that glomerular stretching increases mesangial expansion [226, 239, 242, 243] and that diabetes per se enhances the stretch induced extracellular matrix accumulation [228]. Furthermore mechanical stretching increases the synthesis and activation of the prosclerotic molecule transforming growth factor- β [229]. Transforming growth factor- β is found to be a critical mediator in the net accumulation of extracellular matrix especially in cell culture exposed to high glucose [233, 237]. The above-mentioned changes are ultimately leading to albuminuria and glomerulosclerosis with hyalinosis [169, 226, 241].

Biopsy studies of patients with long-term hypertensive lesions [246] and/or diabetic glomerulosclerosis [32, 247] have revealed severe arteriolar hyalinosis and/or fibrinoid swelling of the intima, these changes is likely to cause further impairment in renal autoregulation [32, 246, 248-250].

The importance of glomerular capillary hypertension in the development/progression of renal disease is supported by the fact that normotension [154, 171, 173, 224, 251] and reduction of glomerular capillary pressure with antihypertensive treatment [245, 252, 253] or low protein diet [226, 227, 239, 242, 254, 255] protects against the development and progression in renal disease in animals.

Combination of the above mentioned animal studies, with studies in patients with diabetic [256] or nondiabetic glomerulopathies [257] have made it generally accepted that lowering of BP with antihypertensive treatment is the keystone in reducing the development and progression in kidney diseases. Furthermore, it has recently been revealed that treatment with AIIA is renoprotective independent of its bloodpressure-lowering effect in microalbuminuric [258] and macroalbuminuric type 2 diabetic patients [259, 260]. From a kidney point of view, antihypertensive treatment that does not impair renal autoregulation, such as AIIA, should therefore be the first drug of choice.

In conclusion, impaired renal autoregulation is part of the pathophysiological changes that leads to albuminuria and glomerulosclerosis with hyalinosis. Antihypertensive treatment is the keystone in reducing the development and progression in kidney diseases. However, antihypertensive treatment not interfering with normal renal autoregulation, such as AIIA, should from a kidney point of view be the first drug of choice.

4. NEPHROPATHY IN TYPE 2 DIABETIC PATIENTS

A) THE NATURAL COURSE OF KIDNEY FUNCTION IN ALBUMINURIC TYPE 2 DIABETIC PATIENTS

The cumulative incidence of diabetic related renal disease in Europe [261-266], the United States [261] and in Japan [261, 267, 268] is approximately 20-45% after 20 [261, 263-265, 268] to 40 years [262, 266, 267] duration of diabetes. Whereas the incidence of diabetic nephropathy in patients with type 1 diabetes seems to be unchanged [261, 265] or decreased over the years [264, 268], the incidence of type 2 diabetic patients with nephropathy tends to increase [268]. Diabetic nephropathy has become the single most important cause of ESRD [269-271]. At least 50% of the ESRD associated with diabetes occurs in type 2 diabetic patients [271-274]. Even though health care problems related to renal disease in type 2 diabetic pa-

tients has become a major burden for the patients and the health care system, most of our knowledge concerning the natural history of diabetic nephropathy originates from studies of albuminuric type 1 diabetic patients.

Mogensen et al [275] performed the first study evaluating the rate of decline in GFR in Caucasian mainly hypertensive albuminuric type 1 diabetic patients who had never received antihypertensive treatment. A highly variable rate of decline in GFR was found (11 (4 to 24) ml/min/year), and a positive correlation was shown between BP and albuminuria, and rate of decline in GFR. Parving et al [276] later confirmed these results. They also revealed a progressive increase in BP and albuminuria, and a variable rate of decline in GFR of 9 (1.2 to 18) ml/min/year. Jacobsen et al [277] demonstrated in a selected group of normotensive albuminuric type 1 diabetic patients a much slower, but still highly variable decline in GFR of 1.2 (-4.4 to 12.9) ml/min/year. The above-mentioned studies all suggests that the level of BP and albuminuria acts as so called progression promoters.

The information on the natural course of kidney function in type 2 diabetic patients not treated with antihypertensive treatment is limited. Baba et al [278] studied five normotensive type 2 diabetic patients and found a rate of decline in GFR of 4.8 (0.7 to 7.0) ml/min/year. Nelson et al [279] studied the natural course of the development and progression of renal disease in Pima Indians with type 2 diabetes mellitus followed for 4 years. Initially patients with albuminuria were not treated with drugs that might alter the course of kidney function, however as the renoprotective effect of ACEI was demonstrated in 1993 [280] 30% of the patients were started on ACEI treatment. In that study, the average decline in GFR was 11 ml/min/year, and urinary albumin-to-creatinine ratio (mg/g) increased from 1180 to 2621 during follow-up. Higher renal plasma flow, albuminuria and body mass index (BMI) at baseline predicted a more rapid decline in GFR, whereas systemic BP and Haemoglobin A_{1c} (HbA_{1c}) values did not.

It is common knowledge, that antihypertensive treatment has a beneficial effect in reducing the rate of decline in GFR in both albuminuric type 1 [281, 282] and type 2 [20, 283-285] diabetic patients, and in preventing development of macrovascular complications [286]. In combination with a high prevalence of hypertension of approximately 90% [287] in type 2 diabetic patients with nephropathy, this knowledge did not, for obvious ethical reasons allow us to conduct a prospective study on the natural history of diabetic nephropathy in an unselected group of albuminuric type 2 diabetic patients. We therefore retrospectively identified all type 2 diabetic patients with diabetic nephropathy who had been or still were attending the out patient clinic at Steno Diabetes Center. Patients with a follow-up period without antihypertensive treatment for more than 2 years, and with at least three determinations of GFR after onset of albuminuria were selected (n=13) [288]. During the follow-up time of 4.6 (2.0 to 8.8) years, a highly variable rate of decline in GFR of 4.5 (-0.4 to 12.0) ml/min/year was revealed (Fig. 9). Due to the small sample size, our results must be interpreted with caution, but they do provide evidence of a rather slow rate of decline in GFR in normotensive to borderline hypertensive type 2 diabetic patients with diabetic nephropathy. We found no significant correlation between the rate of decline in GFR and BP. However, we found a tendency to increasing BP (predominately systolic BP) and albuminuria during follow-up. Other putative progression promoters such as: HbA_{1c}, cholesterol, baseline GFR, known duration of diabetes, BMI, smoking, or age had no significant association with the rate of decline in GFR in our study. Furthermore, the variability in the rate of decline in GFR could hardly be due to heterogeneity in the underlying kidney disease, since we used strict criteria for selection (persistent albuminuria, presence of diabetic retinopathy, and no clinical or laboratory evidence of other kidney or renal tract disease) of patients with diabetic nephropathy [29]. One patient did not fulfil these clinical criteria, but a kidney biopsy showed diabetic glomerulosclerosis.

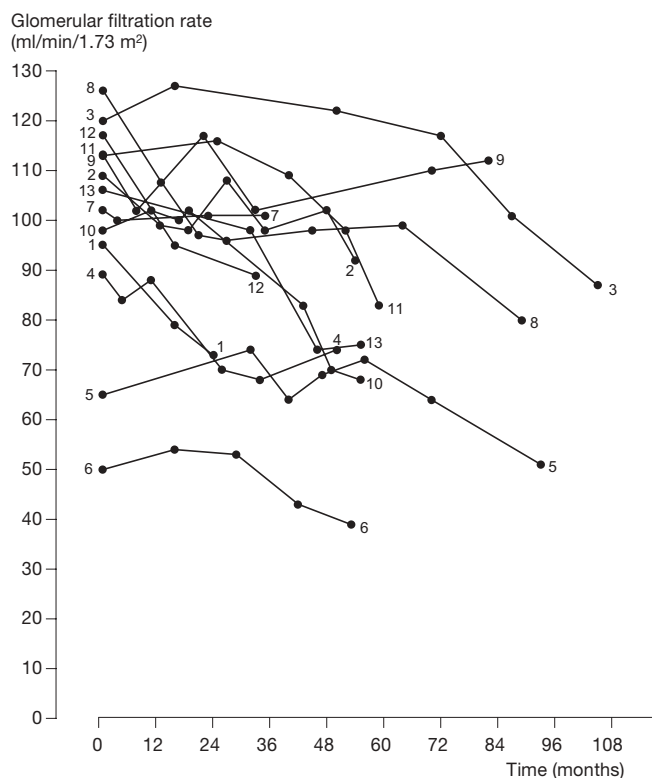


Fig. 9. Individual course of GFR in 13 type 2 diabetic patients with diabetic nephropathy, who had never received any antihypertensive drugs.

The decline in GFR in the Pima Indians was more than twice as high as in our study despite nearly same BP level. Different race and more pronounced elevation in baseline GFR, albuminuria, BMI, and HbA1c in the former study might explain part of the discrepancy. Furthermore glomerular size is nearly two times greater in Pima Indians as compared to Caucasians [289], and increased glomerular size may play an important role for initiation and progression of glomerulopathy [290, 291].

In conclusion, the natural course of rate of decline in GFR in type 1 and type 2 diabetic patients with nephropathy, who never have been treated with antihypertensive drugs, is characterized by a highly variable rate of decline in GFR, which is predominately dependent on the level of arterial BP and albuminuria.

B) CAUSES OF ALBUMINURIA IN TYPE 2 DIABETIC PATIENTS

Whereas only 5% or less of type 1 diabetic patients with persistently elevated UAE have evidence of a nondiabetic kidney disease [292], a much higher and highly variable prevalence of nondiabetic kidney disease has been demonstrated in kidney biopsies as the cause of albuminuria in type 2 diabetic patients [29-31, 34, 293-311] (Table 1). The heterogeneity in prevalence of nondiabetic kidney disease seen in type 2 diabetic patients may partly be explained by differences in geographical and ethnic origin. Furthermore, differences in patient sampling, study design, level of albuminuria and age of the patients adds to the disparity. In particular it is important to stress whether a study reflect selected (biased) or unselected patients groups.

Ethnic origin and geographical differences. The highest rate of nondiabetic kidney disease (81%) has been found in type 2 diabetic patients from India [312]. The majority of the patients suffered from acute infectious glomerulonephritis, which is particular common in tropical area. Even though glomerulonephritis is common in tropical area, the high prevalence of nondiabetic kidney disease in the study of John et al. [312] is based on kidney biopsies from relatively young type 2 diabetic patients who had nephrotic syndrome, unexplained haematuria, proteinuria without retinopathy, rapidly progressive renal failure or unexplained renal failure, and should therefore not be regarded as the prevalence of nondiabetic kidney disease among Indian type 2 diabetic patients with albuminuria.

Nzerue et al. [310] found a prevalence of nondiabetic kidney disease of 58% in African-American type 2 diabetic patients who had severe nephrotic syndrome, suspected nephritis or renal failure atypical for diabetic nephropathy. The most prevalent nondiabetic glomerulopathy was focal segmental glomerulosclerosis. This is in contrast to other biopsy studies including Caucasians, Japanese or Chinese patients where the most prevalent found nondiabetic kidney disease was immunoglobulin A (IgA) nephropathy [29, 302, 308, 313]. These results are in agreement with a higher prevalence of focal segmental glomerulosclerosis in unselected populations of nephrotic African-American patients compared to white patients [314]. In an autopsy study from 1974 including type 2 diabetic Pima Indians, Kamenetzky et al. [293] found that pyelonephritis was the most frequently nondiabetic cause of proteinuria. However the treatment of pyelonephritis has improved over the years, and a change in the prevalence of nondiabetic renal disease among this ethnic group might have occurred, but no new data is available.

Patient sampling and study design. The prevalence of nondiabetic kidney disease is 13-48% in Caucasian type 2 diabetic patients referred to nephrology department for a kidney biopsy [34, 298-300, 306]. This prevalence is based on retrospective and cross-sectional studies (Table 1). The studies have different indications for renal biopsy, however all patients had clinical symptoms/signs suggesting renal disease other than diabetic nephropathy. Richards et al [298] who included mainly type 2 diabetic patients with nephrotic syndrome found a large prevalence, whereas a much lower prevalence was found by Olsen et al. [306] who included patients clinical signs not completely characteristic of diabetic nephropathy. It is evident that such differences in selection of patients might cause bias of the results.

Only one prospective study has included unselected albuminuric type 2 diabetic patients who were attending a diabetic clinic. Parving et al. [29] found a prevalence of 33% of nondiabetic kidney disease in patients less than 66 years of age, 4 (33%) of these patients had normal or near normal glomerular structure. A relatively high prevalence (25%) of albuminuric type 2 diabetic patients with normal glomerular structure has recently been confirmed in a cross-sectional study from Finland [304].

In 1997 Brocco et al. [307] included 53 mikroalbuminuric type 2 diabetic patients in a prospective study and found atypical pattern in 33% of the patients, but no nondiabetic glomerular disease was revealed. In an unbiased clinical trial Cordennier et al. [31] included both albuminuric and microalbuminuric patients and revealed nondiabetic kidney disease in 15% of the patients.

Albuminuria and age. Unfortunately most of the studies evaluating the prevalence of nondiabetic kidney disease lack information on patient age and level of albuminuria. The prevalence of nondiabetic renal disease is likely to increase with increasing age and it is therefore important to know differences in age between studies. Since the prevalence of nondiabetic glomerular structural lesions in microalbuminuric type 2 diabetic patients is close to zero [305, 309, 315], and the prevalence of nondiabetic kidney disease in albuminuric patients is approximately 30% [29, 300, 304, 308, 311], it is even more important to have information on differences in level of albuminuria between studies.

Even though the differences between above-mentioned studies make it difficult to establish the prevalence of nondiabetic kidney disease in type 2 diabetic patients, it is evident that a higher percentage of albuminuric type 2 diabetic patients without retinopathy suffers from nondiabetic kidney disease compared to patients with retinopathy [29, 295, 296, 299, 308], however the exact prevalence of nondiabetic kidney disease in this group of patients without retinopathy is not known.

We evaluated all eligible Caucasian type 2 diabetic patients with persistent albuminuria (>300 mg/24 h), without retinopathy, and with age less than 66 years, who were attending the out patient clinic at Steno Diabetes Centre between 1978-1998 [313]. Fifty-eight of

Table 1. Renal disease in type 2 diabetic patients based on reports in the literature.

Reference	Number	Type of diabetes	Ethnic origin	Patient sampling	Design	Level of albuminuria (mg/24h)	Age (years)	Diabetic glomerulopathy (%)	Normal/near normal structure (%)	Nondiabetic kidney disease (%)
<i>Kamenetzky et al 1974</i>	43	2	Pima Indians	Autopsy	Cross-sectional	normal to albuminuric	62	65.1	?	16.3
<i>Kasinath et al 1983</i>	122	1 + 2	?(USA)	Medical center	Retrospective/cross-sectional	?	?	?(92)	?	8
<i>Chihara et al et al. 1986</i>	69	2	Japanese	Medical center	Cross-sectional	normal to nephrotic	?	67	0	33
<i>Amoah et al 1988</i>	60	2	Caucasian/Black (USA)	Nephrology department	Retrospective/cross-sectional	Dipstick positive	?	72	0	28
<i>Waldherr et al 1992</i>	210	1 + 2	?(Germany)	Autopsy	Cross-sectional	?	74	79	?(20.5)	0.5
<i>Parving et al 1992</i>	35	2	Caucasian	DM out-patient clinic	Prospective/cross-sectional	>300mg	<66	77	11	22
<i>Richards et al 1992</i>	46	2	?(UK)	Renal unit	Retrospective/cross-sectional	normal to nephrotic	54/60	52	0	48
<i>Kleinknecht et al 1992</i>	35	2	?(France)	Nephrology department	?	?	?	60	0	40
<i>Gambara et al 1993</i>	52	2	?(Italy)	Nephrology department	Retrospective	>500	49 to 83	36	(31% atypical pattern)	33
<i>John et al 1994</i>	80	2	India	Nephrology department	Retrospective/cross-sectional	?	47	19	0	81
<i>Suzuki et al 1994</i>	128	2	Japanese	Medical department	Retrospective/cross-sectional	normal to nephrotic	54	84	0	16
<i>Pinel et al 1995</i>	30	2	?(UK)	?	No evidence of nondiabetic kidney disease	70 to 5000	26 to 65	83	(17% non-specific pattern)	
<i>Wirta et al 1995</i>	16	2	Caucasian	Health care center	Population based/cross-sectional	300	?	75	25	0
<i>Fioretto et al et al.1996</i>	34	2	?(Italy)	Diabetic centre	Multicentre study	<300	58	29	29 (41% atypical pattern)	0
<i>Olsen & Mogensen 1996</i>	33	2	Caucasian	Nephrology department	Retrospective/cross-sectional	?	62	87	0	13
<i>Brocco et al 1997</i>	53	2	Caucasian	Diabetic clinic	Prospective/consecutive	<300	58/55/61	26	41 (33% atypical pattern)	0
<i>Mak et al 1997</i>	51	2	Chinese	Renal unit	Prospective	>600	57/50	67	0	33
<i>Firetto et al 1998</i>	32	2	Caucasian	Medical department	In rolled into clinical study	<300	57/51/55	38	31 (31% atypical pattern)	0
<i>Schwartz et al 1998</i>	34	2	?(Multicentre)	?	In rolled into clinical study	>300	57/59	94	0	6
<i>Ruggenti et al 1998</i>	65	2	?(Italy)	Nephrology department	Retrospective/cross-sectional	>100	60	82	0	18
<i>Cordonnier et al et al.1999</i>	26		?(France)	Clinical centres	In rolled into clinical study	70 to 4210	47	85	0	15
<i>Nzerue et al 2000</i>	31	2	African-American	Medical department	Retrospective/cross-sectional	?	?	42	0	58

the patients without retinopathy were referred for a kidney biopsy, but 6 of these patients later decided not to participate and one kidney biopsy did not succeed. The kidney biopsy revealed diffuse (n=34) or nodular (n=1) diabetic glomerulopathy in 69% of the patients. In the remaining 16 patients (31%), normal glomerular structure was found in 9 (18%) and 7 (13%) biopsies had different types of glomerulonephritis. In agreement with other studies [298, 300, 302, 308] it was not possible to predict causes of albuminuria or obtain prognostic information on the kidney disease based on differences in demographic, clinical and laboratory data between the

two groups. The prevalence of patients without diabetic glomerulopathy in our study was, as expected, higher than in most of the above mentioned studies where patients with clinical diabetic nephropathy (persistent albuminuria, presence of diabetic retinopathy, and no clinical or laboratory evidence of other kidney or renal tract disease [29]) were included. It must be emphasized that the sole indication for kidney biopsy in our study was presence of albuminuria and lack of diabetic retinopathy, in other words we had no clinical suspicion of a nondiabetic kidney disease.

Our finding of normal glomerular structure in 18% of the pa-

tients may, however, be a conservative estimate since 15 patients with albuminuria between 300-1000 mg was excluded from the study, because the criteria for performing kidney biopsy was changed during the study period from albuminuria persistently above 300 mg to albuminuria persistently above 1000 mg/24 h.

Albuminuria in some of our patients with normal renal structure may reflect one of the following causes: Minimal-change nephropathy, focal segmental glomerulosclerosis (undetected), silent diabetic glomerulopathy (electron microscopic glomerulopathy) and finally, a hypothetic entity with normal renal structure but increased glomerular permeability to macromolecules (size/charge-defects). Furthermore arteriolar structural abnormalities may lead to impaired vascular responses to changes in systemic BP and thereby contribute to increased leakiness of glomerular filter [82].

In conclusion, type 2 diabetic patients with evaluated UAE, especially in the macroalbuminuric range, have a high prevalence of nondiabetic kidney disease, the prevalence and cause of nondiabetic albuminuria is highly dependent on geographic and ethnic differences. Most studies evaluating the prevalence of nondiabetic kidney diseases suffers from sampling bias, but unbiased studies indicate a prevalence of app. 30% among albuminuric Caucasian type 2 diabetic patients and an even higher prevalence if the patients lack retinopathy. A kidney biopsy is necessary to establish the underlying cause of albuminuria in type 2 diabetic patients without retinopathy. Further studies are needed in order to determine the prevalence of nondiabetic kidney disease in diabetic non-Caucasian populations.

C) RENAL STRUCTURE AND FUNCTION IN ALBUMINURIC TYPE 2 DIABETIC PATIENTS

In patients with kidney disease the morphometric techniques have allowed for quantitations of the structural changes and thereby facilitated correlation of these changes with kidney function.

The structural changes most commonly seen in albuminuric type 1 and type 2 diabetic patients are: GBM thickening, changes in podocyte number and podocyte foot processes, increased mesangium and mesangial matrix leading to loss of filtration surface area, totally sclerotic or occluded glomeruli, hyalinosis, interstitial fibrosis and expansion, and tubular atrophy.

Glomerular filtration barrier, albuminuria and kidney function. Albuminuric type 2 [32, 316-318] and type 1 [319] diabetic patients have increased thickening of GBM. The increased thickening of GBM is associated with increased albuminuria [320]. An association between GBM thickening and loss of kidney function has furthermore been demonstrated in type 2 diabetic patients [317, 318, 321] whereas it is not clear if such an association is present in type 1 diabetic patients [322].

Studies have shown that albuminuria correlate with changes in foot process number and width in type 1 [323] and type 2 diabetic patients [324], and in nondiabetic patients [325]. However, albuminuria can be found in absence of changes in podocytes number and foot process width. While the above-mentioned changes are present in patients with low levels of microalbuminuria, changes in endothelium and filtration slit-length density are only detectable in type 2 [321] and type 1 diabetic patients [326] with high levels of microalbuminuria. The changes in the endothelium and the filtration slit-length density may reduce K_f . This reduction in K_f may result in a decline in GFR.

Mesangium, albuminuria and kidney function. Several studies of type 1 diabetic patients [322, 327-329] with a wide range of albuminuria and with normal to severe renal structural lesions have revealed a correlation between mesangial volume fraction and albuminuria. Our results suggested that a correlation between mesangial volume fraction and albuminuria is also present in albuminuric type 2 diabetic patients without retinopathy irrespectively of the underling cause for albuminuria [313]. However, our study of macroalbuminuric type 2 [313] and a study of microalbuminuric

type 1 diabetic patient [330] have revealed that the mesangial volume fraction can be within the normal level in spite of micro- and macroalbuminuria. These findings indicate that the cutoff point between normal mesangial volume fraction and mild diabetic glomerulopathy is somewhat arbitrary.

A close inverse correlation between mesangial volume fraction and kidney function has been demonstrated both in type 2 [36, 316] and type 1 [322, 327] diabetic patients. We confirmed and extended these findings, by demonstrating a close inverse correlation between mesangial volume fraction and GFR in albuminuric type 2 diabetic patients with and without diabetic kidney disease [313]. Since the structural determinant of kidney function is the total area of the peripheral capillary surface, this relationship probably resulted from the expanding mesangium compromising the structure of glomerular capillaries [292]. In further support of this theory are results suggesting that the peripheral capillary filtration surface per glomerulus is directly related to GFR in type 1 diabetic patients with varying degree of albuminuria [331, 332].

Glomerular vessels, totally occluded glomeruli, albuminuria and kidney function. Hyaline degenerative changes can involve both the afferent and efferent glomerular arterioles in diabetic patients [333]. These degenerative changes might cause impairment of renal auto-regulation and thereby pressure dependent albuminuria and glomerular hypertension, which may induce pathological changes within the glomerulus as described previously. This scenario is in agreement with results suggesting that the severity of arteriolar hyalinosis correlates with the level of albuminuria and GFR [327]. The frequency of more advanced glomerular arteriolar lesions, defined as complete replacement of smooth muscle by hyaline, correlate directly with increased percentage of globally sclerotic glomeruli [334]. We revealed that the percentage of sclerotic glomeruli correlates with the level of albuminuria and GFR in patients with diabetic nephropathy [313]. In sequential biopsy studies, both arteriolar hyalinosis lesions [329] and the number of sclerosed glomeruli progresses as the diabetic kidney disease advances [35]. These observations support the hypothesis that global glomerular sclerosis in diabetic nephropathy might derive in part from vascular pathology. This view is supported by studies indicating that the cortical distribution of global glomerular sclerosis in type 1 diabetic patients fits a pattern consistent with a vasculo-occlusive process. However, presence of sclerosed glomeruli is relatively common in normoalbuminuric nondiabetic persons with normal renal function in the same age as our patients [335]. Furthermore it is possible that interlobar arteriosclerosis is also involved in the vascular impairment of kidney function in type 2 diabetic patients [336]. An additional mechanism in diabetes might be extreme mesangial expansion with consequent capillary closure [337].

Tubulo-interstitial changes, albuminuria and kidney function. Tubulo-interstitial changes might develop as sequelae to arteriolar and arteriosclerosis. Consequently, tubulo-interstitial abnormalities might occur in biopsies with as well as without diabetic glomerulopathy. Studies in type 2 diabetic patients have demonstrated severe tubulo-interstitial changes in absence of or with only mild diabetic glomerular changes in patients with microalbuminuria [305, 307]. In our study albuminuric type 2 diabetic patients with as well as those without glomerulopathy included cases with marked focal fibrosis [313]. However, a correlation between fractional area of focal interstitial fibrosis and tubular atrophy of cortical area and GFR was only revealed in patients without diabetic glomerulopathy. Furthermore the tubulo-interstitial changes did not correlate with the level of albuminuria irrespectively of the underlying cause of albuminuria. Since mesangial expansion is the central element in the development of diabetic glomerulopathy, it is possible that tubulo-interstitial changes at later stages are consequences of the advanced glomerular injury [329]. The advanced glomerular injury may thus overrule the effect of tubulo-interstitial changes on the change in GFR and albuminuria. Mauer et al. [338] have shown that both

hypertension and mesangial expansion increased the tubulo-interstitial injury in albuminuric type 1 diabetic patients. However, Taft et al. [35] reported that the decline in creatinine clearance over time correlated inversely with changes in interstitial fibrosis in a mixed group of albuminuric type 1 and type 2 diabetic patients, while the changes in interstitial fibrosis did not correlate with the level of proteinuria and BP. Furthermore, White et al [318] demonstrated in hypertensive type 2 diabetic patients with proteinuria a close inverse correlation between volume fraction of the interstitium and creatinine clearance, whereas proteinuria only correlate with the glomerulopathy. While the above-mentioned studies all demonstrate lack of correlation between albuminuria and tubulo-interstitial changes, there is disagreement with respect to the impact of tubulo-interstitial changes on kidney function. This disagreement may be related to differences in the measurements of the tubulo-interstitial changes, and differences in BP and antihypertensive treatment that might alter the course of kidney function.

In conclusion, diabetic nephropathy is related to structural changes in the glomerular filtration barrier that leads to a reduction in K_f . Reduction in K_f will induce a reduction in kidney function. Mesangial expansion is closely associated with reduction in kidney function and increased level of albuminuria. The relationship probably results from the expanding mesangium compromising the structure of the glomerular capillaries. The development of renal vascular changes such as hyalinosis might impair renal autoregulation and thereby contribute to the development of glomerulopathy. Tubulo-interstitial changes occurs both in patients with and without diabetic nephropathy. In diabetic patients tubulo-interstitial changes might be related to mesangial expansion and develop as sequelae to arteriolo- and arteriosclerosis. The severity of the tubulo-interstitial abnormalities do not correlates with increasing albuminuria, and the effect on kidney function is still debated. New serial biopsy studies are needed in order to determine the effect of different antihypertensive medications on the progression of renal structural lesions in albuminuric type 2 diabetic patients.

D) COURSE OF KIDNEY FUNCTION IN ALBUMINURIC TYPE 2 DIABETIC PATIENTS WITH OR WITHOUT DIABETIC NEPHROPATHY

As discussed earlier, the prevalence of nondiabetic kidney disease is 5% in albuminuric type 1 diabetic patients, whereas a much higher prevalence is found in albuminuric type 2 diabetic patients [31]. Despite the heterogeneous nature of underlying kidney disease in type 2 diabetic patients with albuminuria, no long-term study has compared the clinical course of GFR in albuminuric type 2 diabetic with or without diabetic glomerulopathy [31, 33-36].

We decided to add information to this important topic, by performing a prospective observational study describing the clinical course of GFR [33] in thirty-four patients previously enrolled in the unbiased cross-sectional biopsy study by Parving et al [29]. Twenty-six patients had diabetic glomerulosclerosis (DG-group), and eight had nondiabetic glomerulopathies (NDG-group). There were no differences in clinical, laboratory or demographic data between the two groups at baseline. More than 75% of the patients received antihypertensive treatment at the end of study. During the 7.7 years of follow-up GFR decreased in the DG-group from 82 to 38 ml/min/1.73 m², with rate of decline in GFR of 5.6 (0.3-21.6) ml/min/year. A slower rate of decline in GFR of 1.3 (0.3-7.6) ml/min/year was found in the NDG-group (Table 2). Six (23%) of the patients in the DG-group developed ESRD, whereas none of the patients in the NDG-group developed this condition. However, the latter group had a better preserved kidney function at the onset of the study. The rate of decline in patients with diabetic glomerulopathy found in our study was comparable with the rate of decline found in previous studies of type 2 patients with clinical diabetic nephropathy [283, 285, 339].

The patients with diabetic nephropathy had a significantly rise in

Table 2. Course of GFR, serum creatinine, albuminuria and arterial blood pressure in type 2 diabetic patients with persistent albuminuria.

	Glomerulopathy		p-value ^a
	diabetic (n=26)	non-diabetic (n=8)	
Follow-up (months)	86 (12-170)	118 (55-163)	ns
Number of GFR measurements	10 (3-20)	12 (7-14)	ns
<i>GFR (ml/min/1.73 m²)</i>			
At entry	82 (24-146)	107 (89-135)	<0.05
At end	38 (2-116)	90 (17-119)	<0.05
p-value ^b	<0.001	<0.05	
Rate of decline	5.6 (0.3-21.6)	1.3 (0.3-7.6)	<0.05
<i>Serum creatinine (μmol/l)</i>			
At entry	92 (51-262)	83 (52-101)	ns
At end	168 (75-1106)	95 (69-239)	<0.05
p-value ^b	<0.001	=0.05	
<i>Albuminuria (g/24h)</i>			
At entry	1.4 (0.3-7.2)	2.2(0.8-8.7)	ns
At end	2.6 (0.1-21.6)	0.8 (0.2-2.5)	<0.05
p-value ^b	<0.05	0.05	
Median during follow-up	1.8 (0.2-7.4)	1.1 (0.2-5.0)	ns
<i>Systolic blood pressure (mm Hg)</i>			
At entry	162±5	141±4	<0.05
At end	154±5	149±6	ns
p-value ^b	ns	ns	
Mean during follow-up	161±4	149±4	0.07
<i>Diastolic blood pressure (mm Hg)</i>			
At entry	96±3	88±3	ns
At end	80±2	83±3	ns
p-value ^b	<0.001	ns	
Mean during follow-up	89±2	88±2	ns

Median (range) and mean±SE indicated.

a) Significance of difference between the two groups, and b) within the two groups.

albuminuria from 1.4 to 2.6 g/24 h, despite BP decreased during follow-up. This pattern was not seen in the NDG-group, they had a significant decrease in albuminuria from 2.2 to 0.8 g/24 h, despite unchanged BP. The significantly more rapid decline in GFR in the DG-group compared to the NDG-group is therefore more likely to be caused by qualitative and quantitative difference in the renal structural lesions rate than differences in extrarenal conditions. This suggestion is further supported by the fact that the different course of decline in GFR in the two groups could not be explained by differences in baseline GFR, nor by differences during follow-up in the following putative progression promoters: arterial BP, albuminuria, serum cholesterol, smoking and glycaemic control.

Ruggenti et al [34] evaluated 153 type 2 diabetic patients admitted to nephrology department because of proteinuria and/or renal insufficiency. Patients with rapidly progressive renal disease, advanced renal insufficiency and contraindications for renal biopsy were excluded. In the patients who were selected for renal biopsy they found typical diabetic glomerulopathy in 30, predominant nephroangiosclerosis in 23 and nondiabetic glomerulopathy in 12 of the patients. The patients were followed for 1.8 year. In this highly selected group of patients there were no correlation between the histological groups and the development of endpoints (combined endpoint was doubling of serum creatinine, dialysis, or transplantation). The main predictor of kidney survival was baseline proteinuria. In the patients with proteinuria <2 g/24 h and in patients with proteinuria >2 g/24 h with limited histological abnormalities endpoints were never reached. These finding is in agreement with our finding [33, 340] of a rate fast rate of decline in GFR in patients with nephrotic range albuminuria.

The most commonly found reason for nondiabetic albuminuria in type 2 diabetic patients is IgA glomerulopathy [313]. Mak et al [311] evaluated and compared type 2 diabetic patients with diabetic glomerulopathy (n=27) to patients with IgA glomerulopathy superimposed on diabetic glomerulosclerosis (n=9). They reported after a

follow-up of 2.6 years that the two groups had comparable rate of decline in creatinine clearance, final serum creatinine and proteinuria.

To explore this topic further, we evaluate the course of GFR in our patients without retinopathy from the cross-sectional biopsy study previously discussed [313]. Forty-nine patients were eligible for this study [340], 34 had diabetic glomerulopathy, 9 normal glomerular structure and 6 glomerulonephritis (predominantly IgA glomerulonephritis). Patients were followed for 7 years. In the DG-group the rate of decline in GFR was 5.3 compared to 3.2 ml/min/year in the NDG-group. The lower rate of decline in GFR in patients with diabetic glomerulosclerosis but without retinopathy as compared to patients with diabetic glomerulosclerosis with retinopathy is not unexpected since a correlation between severity of retinopathy and glomerular structural changes has been reported in type 2 diabetic patients [32]. The relatively fast rate of decline in the NDG-group might be explained by the combination of diabetic glomerulopathy and nondiabetic glomerulopathy seen in some of the patients. Fioretto et al. (personal communication) have measured GFR repeatedly during 4 years (range 1.5 to 6 years) in 64 type 2 diabetic patients with persistent microalbuminuria. The cause of microalbuminuria was evaluated by a percutaneous kidney biopsy. The study revealed that only patients with typical diabetic glomerulopathy (12/64, 19%) had a significant decrease in GFR as compared patients with mainly tubulo-interstitial and arteriolar changes (26/64, 40.5%) and patients (26/64, 40.5%) with normal or near normal renal structure, Δ GFR: -6.4, -0.7 and 2.0 ml/min/year, respectively. Interestingly the microalbuminuric patients with normal or near normal renal structure had an increase in GFR, which is in contrast to our albuminuric type 2 diabetic patients without retinopathy with normal glomerular structure, who had a decrease in GFR [340]. However, a rate of decline in GFR close to the age dependent decline in GFR seen in normal subject was revealed in type 2 diabetic patients who had minimal structural lesion, and low levels of albuminuria combined with relatively low BP.

None of our patients with nondiabetic glomerulopathy received specific treatment (e.g. steroid), but exact knowledge of the underlying cause of albuminuria may play an important role in offering the correct treatment to the patients, as demonstrated in several studies in type 2 diabetic patients suffering from nondiabetic glomerulopathies [294, 296, 341].

Both our studies in albuminuric type 2 diabetic patients [33, 340] showed BP as an independent predictor of the rate of decline in GFR, which is in agreement with studies in both type 1 [256, 342] and type 2 diabetic patients [278, 343].

Several studies have shown that antihypertensive treatment reduces the rate of decline in GFR and thereby postpones ESRD in type 2 [344] and type 1 diabetic patients with albuminuria [18, 19, 345]. Recently, Østerby et al [346] have extended these findings in a sequential biopsy study, by reporting that antihypertensive treatment was capable of slowing the progression of renal ultrastructural changes in diabetic type 1 patients with microalbuminuria. In type 1 diabetic patients with overt nephropathy the effect of antihypertensive treatment on reducing renal structural changes is limited [347]. Unfortunately the observational design of our studies makes it impossible to evaluate the effect of different antihypertensive regimes on the rate of decline in GFR in albuminuric type 2 diabetic patients [33, 340].

Albuminuria is assumed to be an independent risk factor for the progression of renal diseases and a reduction in albuminuria is important to preserve kidney function in type 2 diabetic patients [257, 284, 348, 349]. A close correlation between albuminuria and rate of decline in GFR was demonstrated in our albuminuric type 2 diabetic patients with [33, 340] and without diabetic glomerulopathy [340], which supports the concept that albuminuria is a risk factor for progression in renal disease.

The impact of hyperglycaemia on the progression in diabetic

nephropathy is debated. In agreement with our findings several other studies have failed to demonstrate a significant correlation between glycaemic control and progression of GFR in albuminuric type 2 diabetic patients [279, 343]. In contrast several studies in type 1 diabetic patients have shown that hyperglycaemia is a progression promoter of diabetic nephropathy [350-352] and that long-term normalisation of blood glucose after pancreas transplantation can reverse structural lesion in patients with diabetic glomerulopathy [353].

Both studies in albuminuric type 1 [342, 354] and type 2 diabetic patients [355] have reported that high serum cholesterol is associated with a more rapid deterioration of kidney function. We found no such correlation between the rate of decline in GFR with total serum cholesterol or HDL-cholesterol. To solve this disagreement, it is necessary to conduct a study to evaluate the effect of lipid-lowering therapy on the progression of diabetic nephropathy in hyperlipidaemic type 2 diabetic patients, unfortunately no such study has yet been performed.

The effect of smoking on progression of diabetic nephropathy is debated [288, 342, 356].

In conclusion, the clinical course of kidney function in type 2 diabetic patients with albuminuria is dependent on the underlying kidney disease. Type 2 diabetic patients with typical diabetic glomerulosclerosis have a faster rate of decline in GFR compared to albuminuric type 2 diabetic patients with nondiabetic glomerulopathies. A highly variable course of GFR is found in type 2 diabetic patients irrespective of the underlying kidney disease. In albuminuric type 2 diabetic patients with and without diabetic glomerulosclerosis both systemic BP and albuminuria act as progression promoters.

5. CONCLUSIONS

Autoregulation of renal haemodynamics is a vital component in the overall control of kidney function. Renal autoregulation is complex and involves both an autonomous intrinsic activity of the renal arterioles and the tubuloglomerular feedback system. The inborn ability to alter the activity of the smooth muscle cells in the afferent arteriolar in response to changes in systemic BP is the main regulator of the renal autoregulation system, whereas changes in intra- and extrarenal vasoactive hormones have less importance. However, age, hypertension and some vasoactive hormones may change the renal autoregulation range, but no human studies have yet evaluated the effect of age, hypertension and vasoactive hormones effects on renal autoregulation range. Furthermore the range for normal renal autoregulation in humans is only partly known.

There are disagreements between different animal models of diabetes with respect to the effect of diabetes on renal autoregulation. Our study in normoalbuminuric type 2 diabetic patients did not reveal any impact of short-term changes in glycaemic control on GFR autoregulation, when BP was acutely reduced with clonidine. Future human studies are needed to clarify whether or not diabetes per se impairs renal autoregulation, especially studies of diabetic patients evaluating the effect of increased BP on renal autoregulation is lacking.

Both animal studies and our studies of albuminuric diabetic and nondiabetic patients have revealed impaired renal autoregulation if nephron number is reduced and albuminuria present, irrespectively of the cause of albuminuria. The development of diabetic microangiopathy may indicate that autoregulation is impaired not only in the kidney, but also in many other tissues and organs.

Animal studies suggest that antihypertensive drugs have different effects on renal autoregulation. CCB's abolish, thiazide diuretic impair, whereas ACEI, AIIA, beta-blockers, alpha-blockers, amilorid and loop diuretic treatment have little or no effect on renal autoregulation. We revealed that hypertensive type 2 diabetic patients treated with a dihydropyridine calcium channel blocker displays normal to abolished GFR autoregulation response to acute reduction in BP. Abolished renal autoregulation was related to renal ar-

teriolar vasodilatation during the treatment. In contrast, treatment with an angiotensin II receptor antagonist did not change renal autoregulation in hypertensive type 2 diabetic patients. Similar findings have been revealed with respect to these two antihypertensive drugs effect on autoregulation of cerebral blood flow. Since our studies are the first human studies of the effect of antihypertensive treatment on GFR autoregulation, there is a need for further studies evaluating other antihypertensive medications effect on renal autoregulation in humans.

Impaired renal autoregulation leads to enhanced transmission of the systemic BP into the glomerular capillary network resulting in wide swings in P_{GC} . A reduction in P_{GC} is the key to protection against the development and progression of diabetic nephropathy. Consequently, selection of antihypertensive drugs that blocks the synthesis or actions of AII is important in the prevention and treatment of nephropathy.

The natural course of kidney function in mainly normotensive type 1 and type 2 diabetic patients with nephropathy not receiving antihypertensive treatment, is characterized by a rather slow but highly variable rate of decline in GFR, which is predominantly dependent on the level of systemic BP and albuminuria. In comparison, diabetic patients with elevated BP have a faster rate of decline in GFR.

Studies of type 2 diabetic patients have revealed a highly variable prevalence of nondiabetic kidney disease. This variance is caused by high prevalence of infectious diseases in certain geographic areas, ethnic differences, and sampling bias in most of the studies. In unbiased studies a prevalence of app. 30% among albuminuric Caucasian type 2 diabetic patients and an even higher prevalence if the patients lack retinopathy is reported. IgA glomerulonephritis and normal glomerular structure are the most frequent nondiabetic kidney diseases in Caucasian albuminuric type 2 diabetic patients. It is impossible to establish the underlying cause of albuminuria in these patients without kidney biopsies. More studies are needed to establish the prevalence of nondiabetic kidney disease in non-Caucasian patients.

Kidney biopsy studies in Caucasians have revealed that increased albuminuria and reduction in kidney function is related to structural changes that reduce filtration surface area. The dominating structural changes leading to reduced filtration surface is mesangial expansion, however at a later stage of the development of renal impairment vascular changes might be involved in the final glomerular closure. In diabetic patients tubulo-interstitial damage might be related to mesangial expansion or develop as sequelae to arteriolo- and arteriosclerosis. The severity of the tubulo-interstitial abnormalities do not correlates to increasing albuminuria, and the effect on kidney function is still debated. In our biopsy studies, we furthermore demonstrated that type 2 diabetic patients with typical diabetic glomerulopathy have a tendency to a faster rate of decline in GFR as compared to albuminuric type 2 diabetic patients with nondiabetic glomerulopathy. Whereas both systemic BP and albuminuria act as progression promoters in albuminuric type 2 diabetic patients with and without diabetic glomerulopathy, the degree of glycaemic control, dyslipidaemia and smoking seems to have less importance. Serial biopsy studies are needed to establish if progression in structural lesions can be changed by antihypertensive treatment.

ABBREVIATIONS

ACE	Angiotensin converting enzyme
ACEI	Angiotensin converting enzyme inhibition
AII	Angiotensin II
AIIA	Angiotensin II receptor antagonist
ANP	Atrial natriuretic peptide
ATP	Adenosintriphosphat
BMI	Body mass index
BP	Blood pressure
CCB	Calcium channel blocker

CI	Confidence interval
DG	Diabetic glomerulosclerosis
ESRD	End stage renal disease
GBM	Glomerular basement membrane
GFR	Glomerular filtration rate
HbA _{1c}	Haemoglobin A _{1c}
J _v	Fluid movement
K	Filtration barrier permeability
K _f	Glomerular filtration coefficient
L-NAME	N ^G -nitro-L-arginine methyl ester
MABP	Mean arterial blood pressure
NDG	Nondiabetic glomerulopathies
NO	Nitric oxide
P _{GC}	Glomerular capillary hydraulic pressure
Q _A	Glomerular plasma flow
RBF	Renal blood flow
SNGFR	Single-nephron GFR
TGF	Tubuloglomerular feedback
Type 1 diabetes	Insulin-dependent diabetes mellitus
Type 2 diabetes	Non-insulin-dependent diabetes mellitus
UAE	Urinary albumin excretion rate
V _v (mes/glom)	Mesangium in fraction of the total glomerular volume
ΔP	Transcapillary hydraulic pressure gradient between the glomerular capillary and Bowman space
Δπ	Transcapillary colloid osmotic pressure gradient between the glomerular capillary and Bowman space

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