Diabetic Nephropathy in Type 2 Diabetes Prevention and Patient Management

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It is an irony of medical progress that the renal involvement in diabetes mellitus type 2 had been considered twenty years ago (1) as a benign condition for the kidney without causing renal function loss greater than expected from the "normal" aging process. In contrast, today it has become the single most common cause of end-stage renal disease (ESRD) in the entire Western world (2–4). Apart from the individual human suffering that cannot be expressed in numbers, patients with type 2 diabetes undergoing maintenance dialysis consume significantly more financial resources than those with nondiabetic ESRD. In addition, type 2 diabetic patients do poorly on dialysis and have an excess mortality (5). An interdisciplinary approach is needed for patients with type 2 diabetes and nephrologists must deal with a spectrum of comorbidity besides diabetic nephropathy. The famous Dr. Elliot P. Joslin (1869–1962) stated: "With a missionary zeal, one must convert not only the patient’s mind and soul, but also his doctor to the realization that it is worth the effort to control the disease as shown by the sugar-free urine, normal blood sugar and cholesterol" (6). We posit that a similar approach is also indicated with respect to prevention and treatment of nephropathy in patients with type 2 diabetes mellitus.

Some Factors Involved in the Genesis of Diabetic Nephropathy in Type 2 Diabetes

To understand therapeutic interventions, it is mandatory to briefly provide an (incomplete) review of the salient pathophysiologic mechanisms involved in the genesis of renal disease in diabetes.

Type 2 diabetes is characterized by insulin resistance, i.e., the failure to respond to normal concentrations of insulin, and this is accompanied by compensatory hyperinsulinemia, although the kinetics of insulin secretion are abnormal very early. In later stages, β cell secretion fails to overcome insulin resistance (7). Increased lipolysis with fatty acid release and accumulation of fat in parenchymal organs further aggravate the metabolic disturbance. Insulin resistance is the result of genetic (7) as well as environmental factors. In subgroups of patients with type 2 diabetes, monogenetic causes have been identified, but which genes are responsible for the more common polygenic forms is still unclear (8).

How Do Microvascular Complications, Including Renal Disease, Develop?

Recent evidence suggests that increased superoxide formation after high glucose–induced throughput in the mitochondrial electron-transport chain generates reactive oxygen species, which are involved in the development of diabetic complications (9). Particularly in the development of diabetic nephropathy, proteins modified by glucose or glucose-derived products such as methylglyoxal, i.e., Amadori products, and advanced glycation end products (AGE) play a pivotal role (10). Increased mitochondrial oxygenation of glucose also activates protein kinase C (PKC) (9) and subsequently mitogen-activated protein kinases (MAPK) (11). Transforming growth factor-β (TGF-β) appears to be crucial in the development of renal hypertrophy and accumulation of extracellular matrix (12). Renal hypertrophy is an early event; irreversible changes such as glomerulosclerosis and tubulointerstitial fibrosis are preceded by hypertrophy (12). Parallel to and to some extent concomitant with renal hypertrophy, hyperfiltration and intrarenal hypertension develop in type 1 (10) as well as in type 2 diabetes (13). Both hemodynamic and structural changes are important and are interrelated. For example, high glucose stimulates the synthesis of angiotensinogen and angiotensin II (AngII) (14). This polypeptide exerts hemodynamic as well as trophic, inflammatory, and profibrogenic effects on renal cells (15). On the other hand, shear stress and mechanical strain, resulting from altered glomerular hemodynamics and glomerular hypertension, induce the autocrine and/or paracrine release of cytokines and growth factors (14), which in turn plays a role in genesis of glomerulosclerosis and interstitial fibrosis.

The risk of nephropathy is strongly determined by genetic factors. Cardiovascular disease (16) as well as renal disease (17) cluster within families. A positive family history is clinically useful to identify patients with type 2 diabetes at high renal risk. There has been an intense effort to identify the genes coding for renal risk. The complexity of candidate gene analysis is exemplified by controversial results concerning the insertion/deletion polymorphism of the angiotensin-converting enzyme (ACE). The current majority opinion is that, at least in certain ethnic populations, this polymorphism is associated...
with progression of diabetic renal disease but is not useful to predict development of diabetic nephropathy (18,19). Positional analysis has also identified putative loci associated with higher renal risk, at least in selected populations (20), but the generalizability of the results and the functional role of the hypothetical genes have not yet been clarified.

How to Diagnose Type 2 Diabetes?

Recently, the American Diabetes Association (ADA) recommended diagnosis of type 2 diabetes on the basis of a fasting plasma glucose concentration $\geq 126$ mg/dl (7.0 mmol/L) on two different days or a casual plasma glucose concentration $\geq 200$ mg/dl (11.1 mmol/L) at any time of the day without regard to time elapsed since the last meal (21). In contrast, the WHO continues to recommend oral glucose tolerance testing. A 2-h value $\geq 200$ mg/dl (11.1 mmol/L) is diagnostic of diabetes. The agreement between ADA and WHO criteria is not satisfactory. Many individuals diagnosed with diabetes on the basis of WHO criteria would be missed by ADA criteria (22). The oral glucose tolerance test provides, in addition, prognostic information and identifies individuals with the greatest attributable risk of cardiovascular events and death (22,23). Glucose tolerance is influenced by renal dysfunction and by medication (24). We recommend oral glucose tolerance tests in high-risk populations (Table 1) even when the fasting plasma glucose concentration is normal.

Heterogeneity of Renal Involvement in Type 2 Diabetes

Structural damage to the kidney in diabetes mellitus is usually, but not uniformly (25), reflected by microalbuminuria (MA), i.e., elevated urinary albumin excretion (30 to 300 mg/d) in 24-h urine collections or 20 to 200 $\mu$g/min or $\mu$g/ml in spot urine samples. Some consensus recommendations advise to correct urinary albumin in spot urine for creatinine concentration (albumin/creatinine ratio 2.5 to 25 mg albumin/mmol creatinine) and some to use even separate cutoffs for male and female patients. Because albumin excretion shows high day-to-day variability (VC 30%), MA should be diagnosed only if two of three samples on different days test positive in the absence of confounding factors such as fever, physical exercise, urinary tract infection, uncontrolled hypertension, uncontrolled hyperglycemia, or congestive heart failure. There is a progressive increase of renal (and cardiovascular) risk with increasing albumin excretion rates (26,27). This is true even for urinary albumin concentrations within the upper normal range, so that the cut-off must be interpreted with a grain of salt. Thickening of the glomerular basement membrane causing textural abnormalities and abnormal chemical composition as well as loss of negative electric charges had in the past been thought to be the major cause of MA. More recently, disturbances of the number and function of podocytes and specifically the function of the slit membrane are thought to be at least equally important (28). MA is not only a predictor of future nephropathy (10); it is also associated with increased transcription of genes involved in the genesis of glomerulosclerosis (29), at least in type 1 diabetes. Consequently, MA is evidence of existing nephropathy, not a predictor of future nephropathy. The association between glomerular lesions and MA is less pronounced in type 2 diabetes (25). Fioretto et al. (25) found an overall relation, but some patients failed to have MA despite glomerulosclerosis and conversely approximately 30% of microalbuminuric type 2 diabetic patients had structurally normal glomeruli. The known correlation of MA to cardiovascular events (27) may be explained by the fact that the generalized microvascular and macrovascular complications in type 2 diabetes are also found in the kidney, making MA a mirror of the generalized vascular pathology. There is experimental evidence for a role of AngII in reducing nephrin expression in the slit diaphragm of podocytes (30), thus explaining the BP-independent beneficial effect of angiotensin receptor blockers on MA in type 2 diabetic patients (31). The podocyte appears also to be a key player in the progression of renal disease. Kidney biopsies in Pima Indians with type 2 diabetes and MA showed increased glomerular and mesangial volumes, while subjects with overt proteinuria exhibited broadening of podocyte foot processes and reduced numbers of podocytes (32). Podocyte loss is also found in experimental models of diabetes (33) and in patients with type 1 (34) as well as type 2 diabetes (35) and progressive nephropathy. The dogma of MA as a specific reflection of disturbed glomerular permselectivity has recently come under critique, however, because disturbances of proximal tubular reabsorption of albumin have been shown to be a major component of albuminuria in experimental models (36) and in diabetic patients (37).

Several studies in microalbuminuric patients with type 2 diabetes (25,38) documented that the morphology is much more heterogeneous than in microalbuminuric type 1 diabetic patients. This contrasts with the observations in frankly proteinuric type 2 diabetic patients with impaired renal function in whom one uniformly finds diabetic glomerulosclerosis (39).

It was previously thought (40) that MA is uniformly associated with a decrease in GFR. In contrast, more recent studies (41) showed that this is true mainly for the subgroup of patients exhibiting typical lesions of diabetic glomerulopathy. An Australian group even identified a subgroup of patients with type 2 diabetes and progressive decrease of creatinine clearance.

Table 1. Risk factors for impaired glucose tolerance or latent type 2 diabetes

<table>
<thead>
<tr>
<th>Factor</th>
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<tbody>
<tr>
<td>Overweight</td>
</tr>
<tr>
<td>Treatment-resistant hypertension</td>
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<tr>
<td>High-risk population (African American, Hispanic American, Asian American, Native American, Pacific Islander)</td>
</tr>
<tr>
<td>Triglycerides $\geq 250$ mg/dl and/or HDL cholesterol $\leq 35$ mg/dl</td>
</tr>
<tr>
<td>Women who have delivered a large baby (&gt; 4 kg) or have had gestational diabetes</td>
</tr>
<tr>
<td>Endocrine disease (e.g., acromegaly, Cushing syndrome, hyperthyroidism)</td>
</tr>
<tr>
<td>Normal plasma fasting glucose but known hyperglycemia in the past</td>
</tr>
</tbody>
</table>
Proteinuria

Fast increase in proteinuria (over weeks)

History of nondiabetic renal disease

Nephritic sediment (dysmorphic erythrocytes, acanthocytes, numerous casts, particularly composed of red cells)

History of nondiabetic renal disease

Fast increase in proteinuria (over weeks)

Proteinuria > 5 g/24 h

Albuminuria in the absence of retinopathy

Decrease in renal function in the absence of proteinuria

Fast decline of renal function without obvious explanation

despite no increase in albuminuria (42). Unfortunately there is no information on the underlying renal morphology.

In contrast to type 1 diabetic patients in whom marked diabetic glomerulosclerosis is almost uniformly associated with diabetic retinopathy, the latter is found only in approximately 70% of patients according to the IDNT study (43). It is, however, a powerful predictor of an adverse renal prognosis (44).

There have been reports that one often finds “minimal change” lesions in proteinuric type 2 diabetic patients by light microscopy (45), but it is not perfectly clear whether this constellation reflects early diabetes-related podocyte damage that escapes diagnosis by light microscopy. It has also been claimed that glomerulonephritis is more frequent in diabetic compared with non-diabetic patients. This has been found in neither our autopsy series (46) nor a review of world literature by Olsen and Mogensen (47). Suggested indications for renal biopsy are summarized in Table 2.

Control of Glycemia

Control of glycemia in type 2 diabetic patients with nephropathy represents some peculiar aspects. Why should one aim for optimal glycemic control? Today there is no longer any doubt that tight glycemic control prevents the onset or progression of diabetic nephropathy in type 2 diabetic patients (48,49) as it does in type 1 diabetic patients. In the past, it had been thought that once clinically manifest nephropathy had developed, a point of no return was reached beyond which tight glycemic control failed to prevent the further decline in renal function. Nevertheless recent studies from the Steno Hospital showed that glycemic control had some, although less pronounced compared with tight BP control, effect on the rate of progression (50). The most impressive evidence for the role of hyperglycemia, so far only in type 1 diabetic patients, comes from observations on patients with isolated pancreas transplants in whom delayed reversal of glomerulosclerosis was achieved by prolonged normoglycemia (51). Furthermore, glycemic control affects survival. Wu et al. (52) found that type 2 diabetic patients with poor glycemic control in the last 6 mo before the start of dialysis had much worse survival than patients with good glycemic control, and this is also true in type 2 diabetic patients on dialysis (53).

In the United Kingdom Perspective Study UKPDS (49) no threshold was found for any of the microvascular complications above normal glucose levels (HbA1c > 6.2%). It has therefore been concluded that the lower the HbA1c value, the better. Enthusiasm has to be tempered, however, by the consideration that tight control increases the risk of hypoglycemia. Although the risk of hypoglycemia is less in type 2 diabetes, it does exist in patients with impaired renal function. Nevertheless, even there, a target value of < 7.0 HbA1c should be reached.

A cornerstone of glycemic control is lifestyle modification (54), although the efficacy of this measure diminishes as type 2 diabetes progresses. In most patients, ancillary drug treatment is necessary and the question arises: does the drug that is used for glycemic control matter and does renal function affect dosing and efficacy of the hypoglycemic agents? Table 3 summarizes some important data on currently available oral hypoglycemic agents. There is an increasing tendency in type 2 diabetic patients to aim for tight glycemic control by adopting a regime of multiple daily insulin injections (55) to achieve target HbA1c values < 7%. This is particularly true in the difficult to control type 2 diabetic with impaired renal function. Insulin treatment is obligatory when the patient has intermittent problems such as severe infection or surgery. With the exception of gliclazide and glimepiride, most sulfonylurea compounds (or their active metabolites) accumulate in patients with reduced renal function and may then cause prolonged episodes of hypoglycemia. The insulin-sensitizing agent metformin should not be given at all to patients with reduced renal function, e.g., serum creatinine > 1.3 mg/dl, because of the risk of life-threatening lactic acidosis (56). Metformin should also be discontinued before surgery and administration of contrast media. The alpha-glucosidase inhibitor acarbose and related compounds cause gastrointestinal side effects at a high rate. They interfere with postprandial hyperglycemia; for this reason, they reduce the risk that diabetes develops in patients with impaired glucose tolerance (57). In patients with established diabetes, it has only a limited impact on HbA1c. The new glinides augment postprandial glucose-induced insulin secretion and abrogate postprandial hyperglycemic peaks. Insulin sensitizers (glitazones) stimulate the PPAR-δ receptor. These drugs are fascinating on theoretical grounds, but no data on long-term safety and efficacy are available in patients with renal failure. Glitazones do not accumulate in renal failure.

Control of Dyslipidemia

Even when patients with type 2 diabetes do not have a history of coronary heart disease, the risk of cardiovascular death is higher by a factor of 4 (58). The risk becomes abysmal when diabetic patients are in ESRD or on dialysis (2,59). This has led to the recommendation (60) that in type 2 diabetic patients, LDL cholesterol concentrations should be lowered to values < 100 mg/dl irrespective of the presence or absence of CHD. In these patients, because of their high coronary risk, one should consider treatment with statins as the equivalent of primary coronary prophylaxis. Apart from its effect on CHD, dyslipidemia may also contribute to the progression of diabetic

Table 2. Indications for renal biopsy in albuminuric patients with type 2 diabetes

- Nephritic sediment (dysmorphic erythrocytes, acanthocytes, numerous casts, particularly composed of red cells)
- History of nondiabetic renal disease
- Fast increase in proteinuria (over weeks)
- Proteinuria > 5 g/24 h
- Albuminuria in the absence of retinopathy
- Decrease in renal function in the absence of proteinuria
- Fast decline of renal function without obvious explanation

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Hypertension in Type 2 Diabetes

**Hypertension — Pathogenesis.** Hypertension plays a major role in the onset and progression of diabetic nephropathy as well as in the development of macrovascular lesions. There has been some recent evidence that genetic predisposition to hypertension may predispose to the development of diabetic nephropathy. Strojek et al. (67) noted that BP values were significantly higher in offspring of parents with type 2 diabetes compared with those without diabetic nephropathy. Pre-diabetic individuals with impaired glucose tolerance frequently have hypertension as one facet of the metabolic syndrome. In Pima Indians such pre-diabetic hypertension has been shown to be a predictor of diabetic nephropathy (5 yrs after onset of diabetes) (68). At the time when type 2 diabetes had been diagnosed but acute hyperglycemia had been reversed, abnormal ambulatory BP values (> 130/80 mmHg) or an abnormal circadian BP profile (< 15% nighttime decrease) was noted in 80% of the patients (15). Apparently, an inappropriate decrease of nighttime BP early on is somehow related to the onset of nephropathy, as recently also shown in type 1 diabetes by Lurbe et al. (69). In type 2 diabetic patients, it is also a powerful predictor of cardiovascular death, increasing the risk by a factor of 20 (70). It is also related to the risk of progression to dialysis dependency. Even when diabetic patients are normotensive at baseline, an excessive BP increase may be observed during exercise.

Non-proteinuric type 2 diabetic patients who subsequently develop overt proteinuria and diabetic nephropathy have higher BP values (71), as shown in Table 4.

The pulsatile BP profile in type 2 diabetes is strongly influenced by reduced aortic compliance causing higher peak systolic and lower end-diastolic pressures at any given mean arterial pressure. As a result, the BP amplitude is increased. In such patients, systolic BP is often elevated despite normal diastolic BP values (isolated systolic hypertension). In this context, it is notable that systolic BP is the strongest predictor of progression, strokes, and CV events (72). In diabetic patients with ESRD, a high pulse wave velocity as a surrogate marker for reduced vascular compliance significantly predicted mortality (73). Although the type 2 diabetic patient is usually hypertensive before the onset of nephropathy, nephropathy aggravates the severity of hypertension. It would be beyond the scope of this article to discuss the mechanisms through which renal dysfunction affects BP: mainly sodium retention, inappropriate activity of the renin angiotensin system (RAS), sympathetic overactivity, and impaired endothelial cell-dependent vasodilatation (72). Because these pathomechanisms have consequences for

### Table 3. Drugs to treat hyperglycemia in type 2 diabetes and potential problems in patients with diabetic nephropathy

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Accumulate in renal failure with the exception of glimepiride and gliclazide, prolonged hypoglycemia possible.</th>
<th>Dose reduction for repaglinide in renal failure.</th>
<th>Modest reduction in HbA1c (0.5%).</th>
<th>Only licensed for combination therapy. Some compounds of this novel class exhibit liver toxicity. May aggravate edema and heart failure.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meglitinides</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glitazones</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td></td>
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</tbody>
</table>

nephropathy, but only limited information on this point is available.

Patients with type 2 diabetes have a complex lipid pattern (and this is even more pronounced if patients have diabetic nephropathy) with elevated triglycerides, decreased HDL concentrations, and a concentration of LDL cholesterol that is not significantly different from nondiabetic individuals. Nevertheless, there is an excess of small dense LDL particles that are highly atherogenic. In contrast to type 1 diabetes, optimal treatment of glycemia does not normalize dyslipidemia, and this is presumably explained by the fact that even in the absence of hyperglycemia, pre-diabetic patients with impaired glucose tolerance exhibit this pattern of dyslipidemia as one facet of the metabolic syndrome.

There is now clear evidence for benefit from treatment with statins. In the Heart Protection Study (61), diabetic patients with CHD benefited from treatment with simvastatin as much as nondiabetics. In the WOSCOP study (West of Scotland Coronary Prevention Study), pravastatin therapy in nondiabetic patients even led to a 30% reduction in the hazard of developing type 2 diabetes (62), but this observation has not been consistently confirmed. The beneficial effect of statins on CV events may be mediated, at least in part, through improved endothelial cell function (63). Whether statins are also effective in type 2 diabetic patients with ESRD requires further studies. Because of some unique aspects of atherogenesis in renal failure and the potential role of nonclassical risk factors, this problem is currently being investigated in a controlled trial on dialysed type 2 diabetic patients (64).

Increased triglyceride concentrations would be a priori be a good indication for fibrates. Indeed, in diabetic subjects, gemfibrozil reduced the incidence of cardiovascular events by more than 20% (65) and fenofibrate also reduced progression of coronary lesions (66). Nevertheless, the use of fibrates has not become popular in renal failure patients because of the risk of rhabdomyolysis, particularly when fibrates are used that are partially eliminated by renal excretion.
Table 4. Hypertension preceding manifest nephropathy in type 2 diabetic patients (reference 71)*

<table>
<thead>
<tr>
<th>Later development of proteinuria (n = 63)</th>
<th>Postprandial Blood Glucose (mg/dl)</th>
<th>Systolic BP (mmHg)</th>
<th>Frequency of Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>208 (139 to 295)</td>
<td>164 (105 to 215)</td>
<td>70%</td>
</tr>
<tr>
<td>No development of proteinuria (n = 63)</td>
<td>199 (104 to 272)</td>
<td>149 (122 to 183)</td>
<td>43%</td>
</tr>
</tbody>
</table>

*a Data given as median and range.

the selection of antihypertensive agents, it is for instance important that at similar levels of GFR diabetic patients are consistently more hypervolemic than nondiabetic patients (74), underlining the importance of reduced dietary salt intake and diuretic treatment in the antihypertensive management of diabetic patients with nephropathy. A low sodium diet potentiates the antihypertensive and antiproteinuric effect of AT-1 receptor antagonists in type 2 diabetes (75). An average daily intake of 6 g of NaCl is recommended by the ADA (76).

The role of excessive activity of the RAS, at least of the local system in the kidney, and of the sympathetic system explains why pharmacologic blockade of the RAS and sympathetic system is so effective.

Hypertension is a potent predictor of microvascular (renal and retinal) and cardiovascular (coronary, cerebrovascular, peripheral artery disease) complications of diabetes. Coexistence of hypertension and hyperglycemia dramatically and synergistically increases the risk of these complications (for review, see reference 77). It appears that hyperglycemia “sensitizes” the vascular system to the complications of hypertension. It is beyond the scope of this review to discuss the cardiovascular benefit derived from lowering BP in type 2 diabetic patients, but this has clearly been documented in the UKPDS (78) and Hypertension Optimal Treatment (HOT) studies (79). The justification for such provocatively low target BP, the safety of which had been hotly contested in the past, is reinforced by the results of the Prospective Studies Collaboration (80) that, even which had been hotly contested in the past, is reinforced by the results of the Prospective Studies Collaboration (80) that, even in nondiabetic individuals, the lowest cardiovascular risk is seen at systolic pressures of 120 mmHg.

Prevention of the Onset of Diabetic Nephropathy

A certain consensus has been reached with respect to the recommendations for prevention and retardation of progression of diabetic nephropathy. We refer particularly to the updated Clinical Practice Recommendations of the American Diabetes Association (81).

Table 5 summarizes the relevant information with respect to prevention. A group in Kumamoto documented that intensified insulin treatment prevented onset and progression of diabetic microvascular complications, including nephropathy, in type 2 diabetic patients (48). Similarly, the UKPDS found that intensified glycemic control achieving an average HbA1c of 7% decreased the overall rate of microvascular complications (retinopathy and nephropathy) by 25% irrespective how normoglycemia was achieved (49).

There is no doubt that smoking increases not only the risk of onset of type 2 diabetes; it also increases the risk of development of microalbuminuria and further progression of diabetic nephropathy in type 2 diabetic patients (82). This is true even when patients are on ACE inhibitors and have achieved adequate BP control (83). Consequently, nephrologists should not remain passive, but constantly point out the adverse effects of smoking to their patients. Behavioral therapies combined with nicotine strips, antidepressants (84), and in the future possibly nicotine vaccines (85) should be considered.

It is not yet definitely established whether antihypertensive treatment and particularly pharmacologic blockade of the RAS prevent the onset of diabetic nephropathy, although some data are very suggestive indeed (86,87). This point has become largely academic, however, because according to the results of the HOPE and LIFE studies even non-microalbuminuric type 2 diabetic patients should be managed with ACE inhibitors or angiotensin receptor blockers to prevent cardiovascular events.

Although there are no controlled data, there is little doubt that obesity is a potent renal risk factor (88) and this is true in type 2 diabetes as well.

The results of the observational EURODIAB trial show that excessive protein intake is correlated to the degree of microalbuminuria (89), but there is little hard evidence for a beneficial effect of dietary intervention. In later stages of diabetic nephropathy, protein intake seems to affect CV endpoints, but paradoxically not the rate of progression (90). The ADA recommends a protein intake of 0.8 to 1.0 g/kg body weight per day for patients with type 2 diabetes with microalbuminuria and 0.8 g/kg body weight per d in individuals.
with overt nephropathy (76). When recommending low-protein diets, it is indispensable to guarantee adequate intake of calories (30 to 35 kcal/kg per day) to maintain good nutritional status, especially in patients with preterminal renal failure who are at risk of catabolism (91). Close follow-up of these patients is recommended to avoid malnutrition. The danger of malnutrition is illustrated by the fact that in dialysis patients low body mass index predicts poor survival (92).

Various anaglesics have an adverse influence on progression, and a recent study from Sweden showed that even acetaminophen and aspirin dose-dependently increased the risk of chronic renal failure (93).

**Prevention of Progression**

Monitoring of type 2 diabetic patients for microalbuminuria at least once per year is recommended. Microalbuminuria in type 2 diabetic patients is not as potent a renal risk predictor as in type 1 diabetic patients, but it is certainly the best available tool to identify patients in need of intensified treatment (94). To prevent progression in microalbuminuric or proteinuric patients, it is important to adopt an integrated approach, comprising tight antihypertensive control, including pharmacologic blockade of the RAS by ACE inhibitors or angiotensin receptor blockers, intensified glycemic control, cessation of smoking, body weight reduction when appropriate (91), and dietary sodium restriction. As shown in Table 6, the loss of GFR was greater in diabetic patients (111). Although amlodipine was shown to accelerate the loss of GFR in proteinuric patients with renal disease (109), this does not mean that CCB are generally contraindicated in proteinuric patients with renal disease (109). Amlodipine did not increase the renal risk compared with placebo in the IDNT trial (43). Ruggenenti et al. (112) had also shown that in proteinuric patients with impaired renal function, proteinuria, and loss of GFR were on average higher in patients on CCB, but this was no longer the case when patients concomitantly received ACE inhibitors and had mean arterial pressure values well below 100 mmHg. Consequently, CCB are excellent partners in the multi-drug approach to control hypertension in type 2 diabetes, but the first medication should be a drug interfering with the activated RAS.

**New Therapies on the Horizon?**

Although the renal risk in diabetic nephropathy can be reduced by 20 to 40% (IDNT and RENAAL), the fact remains that 70% still progress, justifying attempts to develop novel

### Table 6. The impact of intensified multifactorial intervention in patients with type 2 diabetes (reference 95)

<table>
<thead>
<tr>
<th>Changes in parameters</th>
<th>HbA1c (%)</th>
<th>Total Cholesterol (mmol/l)</th>
<th>Urinary Albumin (mg/24 h)</th>
<th>GFR (ml/min per 1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard treatment (n = 76)</td>
<td>0.2</td>
<td>−0.2</td>
<td>+10</td>
<td>−13</td>
</tr>
<tr>
<td>(± 1.9)</td>
<td>(± 1.3)</td>
<td>((-26 \text{ to } 110))</td>
<td>(± 15)</td>
<td></td>
</tr>
<tr>
<td>Intensified treatment (n = 73)</td>
<td>−0.8</td>
<td>−0.6</td>
<td>−22</td>
<td>−11</td>
</tr>
<tr>
<td>(± 1.6)</td>
<td>(± 0.9)</td>
<td>((-51 \text{ to } 18))</td>
<td>(± 20)</td>
<td></td>
</tr>
<tr>
<td>(P)</td>
<td>0.0001</td>
<td>0.0002</td>
<td>0.0002</td>
<td>NS</td>
</tr>
</tbody>
</table>
therapeutic approaches. Many such treatments work well in animals (interference with TGF-β expression, blocking the effect of AGE, antioxidative therapy), but the clinical effects of experimental approaches are, at best, limited. Some innovative strategies have been clinically tested on small numbers of patients. As an example, the glycosaminoglycan sulodexide was given to nephropathy patients with type 1 and type 2 diabetes for 4 mo (113). Albuminuria was reduced, seemingly additive to ACE inhibition. Whether this will translate into prevention of progression remains to be seen. Clinical evidence suggests a relationship between inflammatory markers such as C-reactive protein and development of diabetic nephropathy (114), but we do not know whether anti-inflammatory interventions will be effective. Exciting though these novel approaches are, they should not detract from the down-to-earth task of providing the best available treatment to diabetic patients with nephropathy. We believe that diabetic nephropathy and its progression could at least be effectively slowed down, if not prevented, in the majority of patients with type 2 diabetes once the above-mentioned standard treatments were implemented in daily clinical practice.

Conclusion

The exponentially increasing number of patients with type 2 diabetes who have a doomed prognosis requires that a state-of-the-art multidisciplinary approach is brought to bear on this problem. The best would be to prevent the development of type 2 diabetes by banning all fast food restaurants. Yet, even in patients with diabetes, it is possible to prevent diabetic nephropathy and reduce progression of established nephropathy. Excellent metabolic control and lowering of BP to very low values are the keystones of therapy. Nephrologists should be involved early in the care of diabetic patients and play a pivotal role in diagnosis, prevention, and treatment of diabetic nephropathy.

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