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REVIEW

Diabetic Kidney Disease: A Syndrome Rather Than a Single Disease

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■ Abstract

The term “diabetic kidney” has recently been proposed to encompass the various lesions, involving all kidney structures that characterize protean kidney damage in patients with diabetes. While glomerular diseases may follow the stepwise progression that was described several decades ago, the tenet that proteinuria identifies diabetic nephropathy is disputed today and should be limited to glomerular lesions. Improvements in glycemic control may have contributed to a decrease in the prevalence of glomerular lesions, initially described as hallmarks of diabetic nephropathy, and revealed other types of renal damage, mainly related to vasculature and interstitium, and these types usually present with little or no proteinuria. Whilst glomerular damage is the hallmark of microvascular lesions, ischemic nephropathies, renal infarction, and cholesterol emboli syndrome are the result of macrovascular involvement, and the presence of underlying renal damage sets the stage for acute infections and drug-induced kidney injuries. Impairment of the phagocytic response can cause severe and unusual forms of acute and chronic pyelonephritis. It is thus concluded that screening for albuminuria, which is useful for detecting “glomerular diabetic nephropathy”, does not identify all potential nephropathies in diabetes patients. As diabetes is a risk factor for all forms of kidney disease, diagnosis in diabetic patients should include the same combination of biochemical, clinical, and imaging tests as employed in non-diabetic subjects, but with the specific consideration that chronic kidney disease (CKD) may develop more rapidly and severely in diabetic patients.

Keywords: diabetes · chronic kidney disease · diabetic nephropathy · glomerulosclerosis · glomeruli · retinopathy

1. Introduction

Diabetic nephropathy is a complex and multifaceted condition that can also be described as a syndrome with varying clinical manifestations and responses to therapy. It is related to different underlying pathophysiological mechanisms and to the effects of the different and changing treatments of diabetes itself [1-5].

The classic term “diabetic nephropathy” points to the presence of a single, well defined, and identifiable kidney disease. Because of the complexity and heterogeneity of renal impairment in diabetic patients, the classic term has been increasingly replaced by the more generic term “diabetic kidney disease” which is reminiscent of the term “chronic kidney disease”. There are also other definitions in the context of kidney disease, including “diabetic glomerulopathy” and “diabetic podocytopathy”, but they limit the field to a specific type or pathogenesis of kidney injury [6-14]. In this review, we use the classic term “diabetic nephropathy” to identify

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the typical progressive glomerular nephropathy in its stages and variants, while the term "diabetic kidney disease" is used in cases where kidney involvement affects other renal structures such as interstitium or blood vessels.

Over the past twenty years, the development and manifestation of diabetic nephropathy have changed, mainly because of improvements in diabetes treatment. In recent times, more attention has been given to type 2 rather than type 1 diabetes. While the original paradigm of diabetic nephropathy was first described in type 1 diabetes, nowadays the disease is more prevalent in type 2 diabetes, which is mainly ascribed to prolonged life expectancy of type 2 diabetes patients [4-5, 15-21].

Abbreviations:
ACE – angiotensin-converting enzyme
ADC - apparent diffusion coefficient
AFOG – acid fuchsin orange G
AIDS – acquired immune deficiency syndrome
AKI – acute kidney injury
ARB – angiotensin receptor blocker
CKD – chronic kidney disease
COX-2 – cyclooxygenase 2
CT – computed tomography
ERA-EDTA – European Renal Association / European Dialysis and Transplant Association
FSGS – focal segmental glomerulosclerosis
GFR – glomerular filtration rate
LDH – lactate dehydrogenase
MRI – magnetic resonance imaging
PAS – periodic acid-Schiff
PTH – parathyroid hormone
RAAS – renin-angiotensin-aldosterone system
UAE – urinary albumin excretion

2. Disease of the "survivors": a parallel to dialysis

At the beginning of the 1980s, it was almost unexpected that dialysis patients survived the first decade of treatment. At the same time, a series of studies were conducted that attempted to identify the clinical and psychological features of the "best candidates" for long-term renal replacement therapy [22-25]. Two main issues emerged from these early studies:

1. The dialysis population had changed over time; the changes reflected the broader acceptance of elderly (attributed to increased life span in the overall population) and "high-risk" patients (diabetic patients were the prototype) [15-21, 26-29].
2. The treatment modified the clinical histories, and as a result of iatrogenesis or incomplete correction of uremia by dialysis, long-term survivors on dialysis presented with disease combinations that otherwise were exceptional [30-33].

Improvements in diabetic care increased survival rates. In younger type 1 diabetes patients, the improved survival prognosis caused a greater acceptance for treatment in dialysis facilities, which previously had not accepted younger patients because of the possible associated cardiovascular impairment. Increased long-term survival was achieved more frequently, at least in selected cases [34-40].

In the 1990s, diabetes patients became the predominant dialysis population, mainly because of the increase in type 2 diabetic patients. Due to the established longer survival in the predialysis phase, these patients could gain additional time until end-stage renal disease [4-5, 15-20, 41-43].

The increased availability of kidney and pancreas transplants further changed the perspectives and management of diabetic patients with severe kidney disease, especially of those with type 1 diabetes. In the 1990s, researchers developed the idea of early combined kidney-pancreas transplantation at a stage in which it was possible to stop the progression of the concomitant retinal and neural damages [44-48].

In contrast, type 2 diabetes patients were frequently affected by "atypical" nephropathies, with combinations of early onset proteinuria (often explained as being due to undiagnosed kidney disease), scarce proteinuria, and diffuse vascular disease, or by a "stepwise" decrease in renal function that did not fit well with the classic description of the four stages of diabetic nephropathy. Typical lesions in diabetic patients coexisted with little proteinuria, while several authors reported non-diabetic kidney diseases as being more common [49-53].

The increase in type 2 diabetic patients visiting nephrology facilities was in part unexpected as it was the main goal of the so-called "Saint Vincent Declaration" (signed by a panel of European diabetes experts in 1989) to reduce end-stage diabetic nephropathy by one-third in five years [5, 16, 54-56]. However, the increase may be explained by improved survival and longer continuance in the dialysis stage before end-stage renal disease is reached. A similar phenomenon was observed in the overall dialysis population that continued to increase mainly because elderly patients with ma-

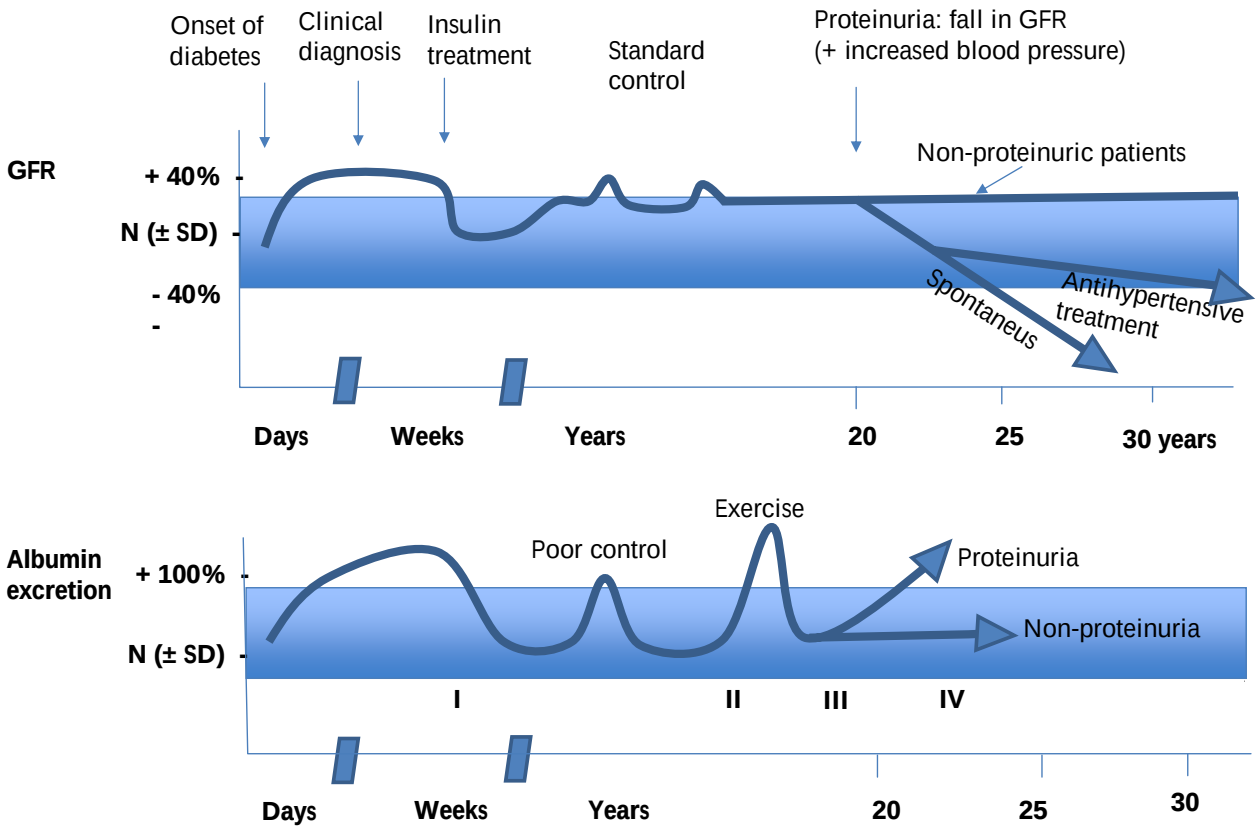

Figure 1. Stages of diabetic nephropathy. Figure creation according to the classic description of the stages of diabetic nephropathy by Mogensen *et al*. [63].

jor comorbidities survived long enough to develop end-stage renal disease [27-29].

Almost 40 years after the widespread acceptance of diabetic patients in the dialysis programs, the increase in elderly patients on dialysis, a subset in which diabetic patients are highly represented, re-posed clinical and ethical problems associated with end-of-life issues and the difficulty in defining the limit between optimal care of frail patients and aggressive treatment [34-37, 57-62].

3. The profile of diabetic nephropathy in type 1 diabetic patients

In their seminal work published in the early eighties, Mogensen and co-workers have developed a model describing the clinical history of nephropathy in type 1 diabetic patients over a course of five stages. Since then, it has been a referral model for assessing the progression and prognosis of diabetic nephropathy [63]. **Figure 1** illustrates the five stages of renal damage in type 1 diabetes according to the model by Mogensen and co-workers:

Stage 1: Early hyperfunction and hypertrophy, occurring before the start of insulin treatment; this condition is partly reversible by insulin treatment [63-64]. After this transitional phase, which can be avoided by starting timely and effective treatment, it follows a clinically "silent" stage 2.

Stage 2: In the original paper, the authors stated that this phase is "characterized by morphologic lesions without signs of clinical disease. However, kidney function tests and morphometry on biopsy specimens reveal changes". These changes include increased glomerular filtration rate (GFR) and albuminuria after physical exercise, which may be more prevalent

in cases of poor diabetes control. The changes determined by kidney biopsy, which were initially reported by Osterby and co-workers and later confirmed by other groups, include thickening of the glomerular basement membrane and mesangial expansion; the latter is considered to be the hallmark of early diabetic nephropathy [65-70].

Albeit of great pathophysiological interest, these findings are of limited clinical use for the following reasons (as also stated in the original report):

1. This condition is not necessarily progressive such that several patients may remain in stage 2 throughout their lives.
2. The functional pattern is unremarkable such that kidney biopsy is not needed.

However, kidney biopsy may indeed be needed in the subsequent stages 3 and 4, especially in the case of early onset of renal damage.

Stage 3: Regarded as incipient diabetic nephropathy. Urinary albumin excretion (UAE) increases. It is thus also called the "microalbuminuric" phase. This stage merges into stage 4.

Stage 4: Overt diabetic nephropathy, with UAE slowly and gradually increasing over the years together with blood pressure. Stage 4 is characterized by persistent proteinuria (>0.5 g/24 h).

Microalbuminuria is thus the first sign of "true" diabetic nephropathy. Many authors still maintain this definition, in particular in specific situations such as pregnancy [71-74]. In the same paper, Mogensen and co-authors defined that diabetic nephropathy is present if blood pressure is high and untreated and GFR declines with a mean rate of about 1 ml/min/month [63].

Stage 5: End-stage renal failure.

In the Mogensen model, the development of overt proteinuria is accompanied by an increase in blood pressure; proteinuria (going up) and kidney function (going down) virtually cross. Afterwards, kidney failure occurs quickly. It is assumed that the process of decline in kidney function takes about 7.5 years from "normal" kidney function (GFR 100 ml/min) to end-stage renal disease (GFR 10 ml/min).

Controversy exists regarding the reversibility of microalbuminuria; the results of several studies over the last few decades remain inconclusive. The condition is potentially responsive to ACE inhibitors, angiotensin II receptor inhibitors, and their combination, but progressing obesity counteracts the effectiveness of this treatment strategy. It is alarming how many young diabetic patients are affected by obesity. Another treatment option is therefore to decelerate the progression of diabetic nephropathy through the restriction of protein intake [75-89].

Although the natural history of diabetic nephropathy, as reported over 30 years ago, has changed mainly because of the disease-modifying effects of therapy, some points still hold true. In the classic view of diabetic nephropathy, the microalbuminuric phase is followed by normalization of the GFR, which is considered the first sign of reduced nephron mass that is no longer able to accomplish a "hyperfiltration" response [63]. If GFR normalization is not linked to optimal diabetes control, it still represents the first sign of decreased renal functional reserve. Therefore, close attention should be paid when loss of GFR is relatively fast, regardless of baseline levels [90-91]. Interestingly, a similar interpretation was proposed for focal segmental lesions in obesity, a condition that is often associated with type 2 diabetes and the metabolic syndrome [92-95].

Nevertheless, the Mogensen model still applies to kidney disease in the setting of poorly controlled type 1 diabetes. Indeed, the natural history and sequence of normo- to micro- to macroalbuminuria has been integrated in the new classification of diabetic nephropathy published in 2014 [96].

4. Characteristics of the renal lesions in diabetic nephropathy

The main glomerular renal lesions in type 1 diabetes include a nodular, classical Kimmelstiel-Wilson lesion, a diffuse pattern, and the presence of non-specific exudative lesions [97-100]. Today, the accumulation of extracellular matrix is considered an indication of nephropathological changes. This accumulation may lead to mesangial expansion and reduction of filtration surface area, which is further disrupted by the thickening of glomerular basement membranes [69, 101-108]. Concomitant changes at the arteriolar level and in the renal interstitium contribute to the overall func-

tional impairment. As in other primary kidney diseases, the severity of the vascular and interstitial lesions bears a strong negative effect on prognosis. The recent pathologic classification by Tervaert and the Renal Pathology Society does not differentiate between type 1 and type 2 diabetes, but provides a comprehensive effort to classify renal lesions from the mildest to the worst ones (**Figure 2**) [109].

Figure 2 illustrates the four classes of diabetic nephropathy according to the extent of the pathologic findings [109]:

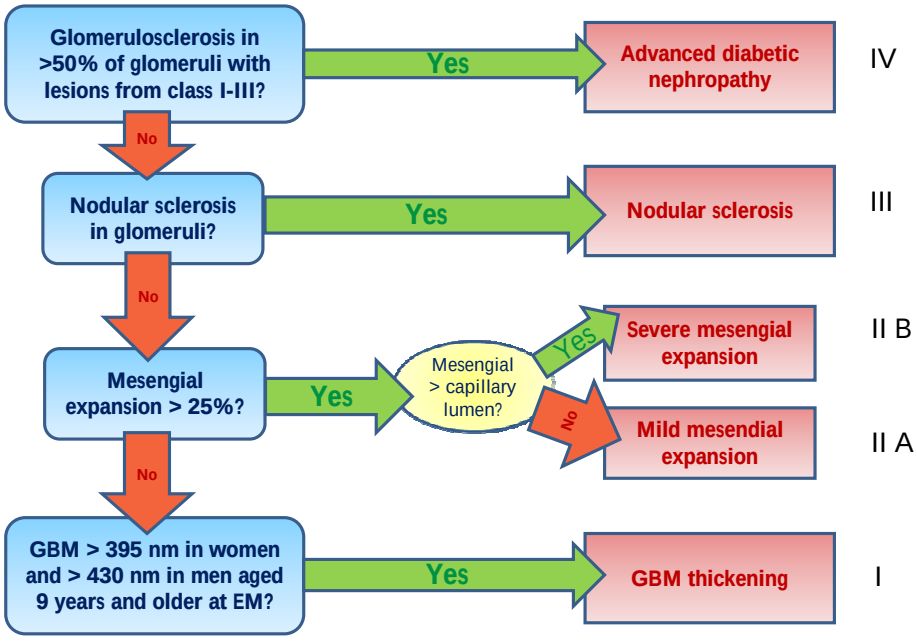

Figure 2. Pathologic classification of diabetic nephropathy. GBM: glomerular basement membrane, EM: electron microscopy. Figure inspired by Tervaert *et al*. [109].

Class 1: Isolated glomerular basement membrane thickening and mild, nonspecific changes, observable by light microscopy, at an extent at which they may not be applicable to the criteria of the other classes.

Class 2: Mesangial expansion, classified as mild or severe, but without nodular sclerosis or global glomerulosclerosis in more than 50% of glomeruli (class 2a: mild; class 2b: severe).

Class 3: Presence of nodular sclerosis in at least one glomerulus (Kimmelstiel-Wilson), without changes as described in class 4.

Class 4: Advanced diabetic glomerulosclerosis involving more than 50% of glomeruli.

Although controversial, the Tervaert classification is simple and incorporates prognostic factors. Also, the importance of its role was confirmed in a large recent case series, involving long-term follow-up investigations of diabetic patients [110-112].

Figure 3 shows examples of diabetic nephropathy in type 1 diabetic patients from Sardinia, a region with one of the highest incidence of type 1 diabetes world wide [113-115].

5. The "renal-retinal syndrome" and indications for kidney biopsy

As healthcare improved over time, type 2 diabetic patients survived long enough to become afflicted with diabetic nephropathy. Therefore, the first microscopic examinations of diabetic kidneys were performed at autopsies of these patients. In most cases, these patients died of cardiovascular diseases. Eight patients aged 48-68 years were described by Kimmelstiel and Wilson in 1935; these patients had a 3-15 year history of diabetes [116-117].

Once the first survivors of juvenile diabetes reached 10-15 years of follow-up, diabetic nephropathy became one of the most dangerous long-term complications of diabetes, tantamount to a disease of young diabetics. In type 2 diabetes, the role of diabetic nephropathy was overlooked for many decades [118-120].

There is still controversy regarding the question of whether to perform renal biopsy in all patients with diabetic nephropathy. In any case, the history of diabetic nephropathy in type 1 diabetes showed that there are atypical cases, which should undergo a different diagnostic pathway and include kidney biopsy [121-125]. Classically, the following five major criteria to identify atypical courses are reported:

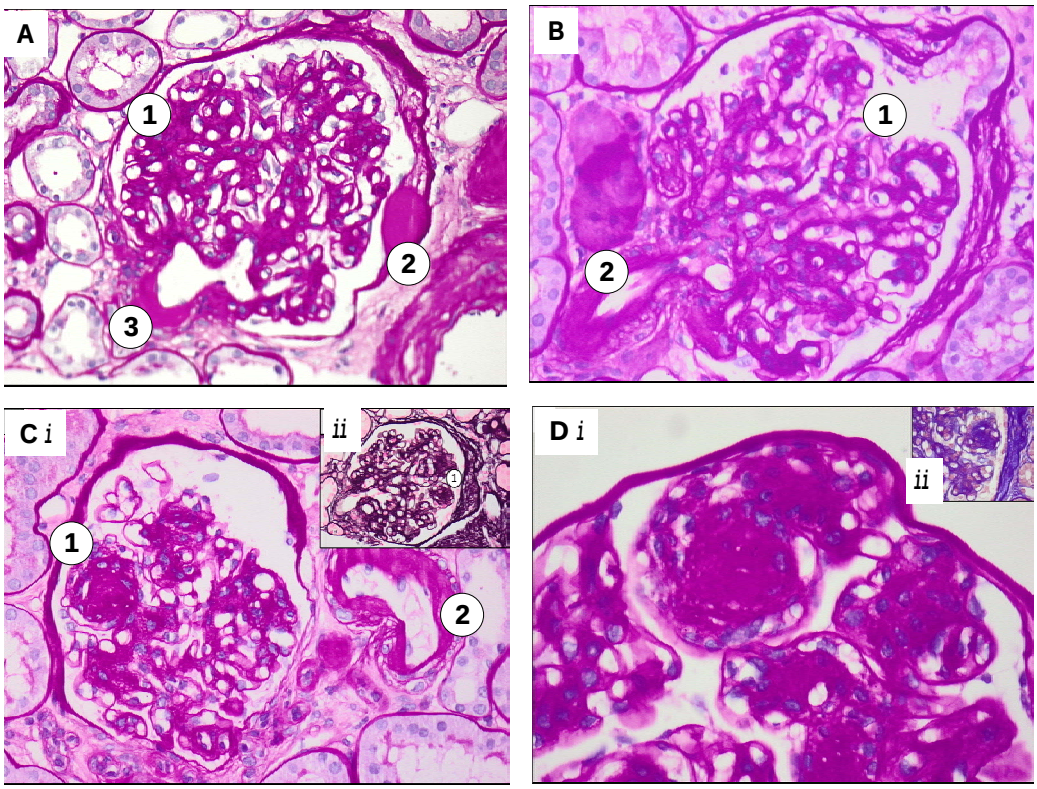

Figure 3. Examples of diabetic nephropathy in diabetic patients in Sardinia. Sardinia is one of the regions with the highest incidence of diabetes in the world. **A**: Periodic acid-Schiff (PAS) 20 X. Diffuse glomerulosclerosis (1) with "capsular drops" from exudative lesions (2) and arteriolar hyalinosis (3). **B**: PAS staining, 20 X. Diffuse mesangial expansion with sclerosis (1) and arteriolar hyalinosis (2). **C**: *i*) PAS 20 X. Diabetic glomerulosclerosis, with nodular pattern (1). Arteriolar hyalinosis (2). *ii*) Methenamine silver 20 X. Diffuse and nodular glomerulosclerosis. **D**: *i*) Periodic acid-Schiff (PAS) 40X. Magnification of nodular glomerulosclerotic lesion surrounded by mesangial cells. *ii*) Acid fuchsin orange G (AFOG) 40 X. Diffuse and nodular sclerosis in diabetic nephropathy.

1. Timing
2. Velocity of progression
3. Hematuria
4. Absent or low proteinuria
5. Absence of retinopathy [121-124, 126-130]

However, in routine clinical care it appeared that these criteria could not perform adequately in order to differentiate non-diabetic from diabetic nephropathy. This problem particularly referred to the increasing population of type 2 diabetic patients, where non-diabetic renal disease has increasingly been recognized [121, 127-135]. Furthermore, relating to the diagnosis of diabetic nephropathy, the morphological stage was not fully predictable by the clinical patterns. In detail, the basic principle applied was: diabetic nephropathy (defined as persistent microalbuminuria) usually occurs at least 10 years after the onset of type 1 diabetes. However, this is not equivalent to type 2 diabetes, where proteinuria is regarded as a marker of cardiovascular morbidity [136-140].

Hallmarks of non-diabetic nephropathy in type 1 diabetes patients include:

- A shorter interval between diagnosis and onset of renal disease.
- A stepwise or rapidly progressive increase in proteinuria or a decrease in kidney function.
- Hematuria without or with low-grade proteinuria [121-125, 127-135, 137-142].

There are also exceptions from these criteria. The exceptions concern patients with atypical appearance of retinal and renal signs, which were once considered to be almost synchronous [143-146]. However, the association between renal and retinal disease is still regarded as close, with pre-

dicting power of diabetic retinopathy for the initiation of diabetic nephropathy [147]. Therefore, the combined consideration of both conditions as renal-retinal syndrome is still warranted. Due to the coincidence of renal and retinal diseases in diabetic patients some authors, interestingly including W.J. Kolff, the inventor of the artificial kidney, regarded dialysis in diabetic patients as a mere "palliative measure with little likelihood of long-term survival or improvement in quality of life" [34].

Despite the general agreement that renal biopsy is the gold standard for diagnosis and classification of diabetic nephropathy, some authors suggested different approaches, ranging from biopsy in all cases to the definition of selected subsets where biopsy should be performed. The proposed strategies may be summarized as follows:

1. All diabetic patients with kidney damage should undergo renal biopsy.
2. Only patients with suspicion of other nephropathies should undergo renal biopsy.
3. Only patients in whom the finding of a different kidney disease would lead to a specific treatment should undergo renal biopsy [53, 148-151].

In this regard, it is important to note that imaging profiles of kidneys in patients with advanced diabetic nephropathy may present without pathological findings (**Figure 4**).

In the past, attention was given to the presence of overt nephropathy only, and other signs of diabetic end-stage kidney disease were frequently disregarded. Today, attention is focused on the onset and progression of CKD, even in the light of good glycemic control, and on the impairment of kidney function that occurs without overt albuminuria. These newer approaches aim to take into account alternative pathogenic pathways that may occur in some cases of CKD. Another important aspect still under investigation is the interplay between genetic background and epigenetic mechanisms, including DNA methylation, histone post-translational modifications in chromatin, and non-coding RNAs [152-156]. Different levels of hyperglycemia, their interplay with growth factors, and oxidant and inflammatory stress can alter gene expression in target cells, including podocytes and renal endothelial cells [154-156]. These alterations are persistent, and they are the basis of a "metabolic memory", by which previous, possibly unrecognized hyperglycemia may induce modifications that persist even after normoglycemia is restored.

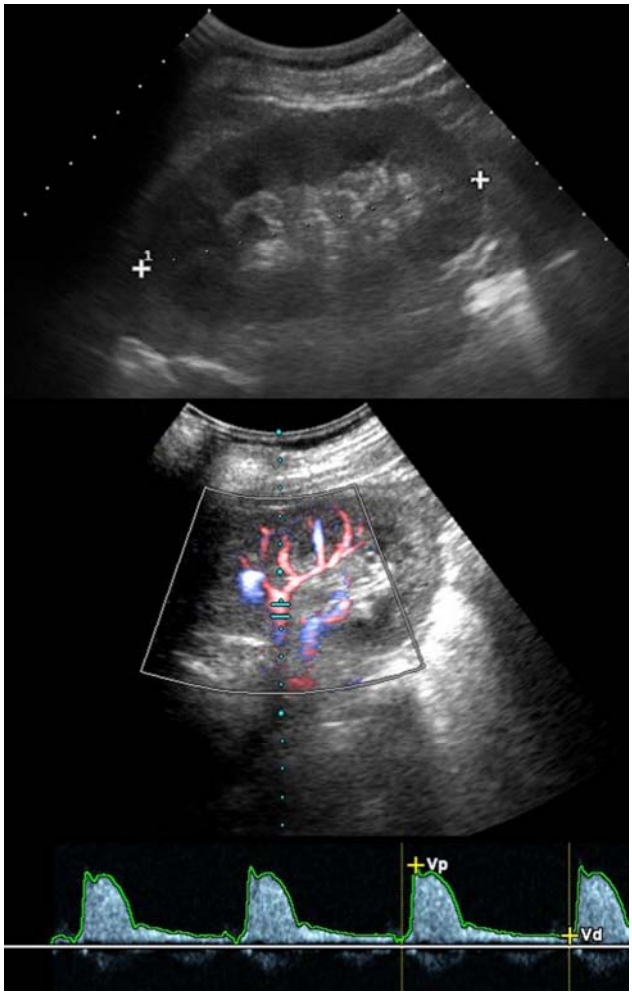

Figure 4. Examples of diabetic nephropathy. The figure shows ultrasound images of a 50-year old type 1 diabetic patient with severe renal failure. Ultrasonography (upper image) shows normal appearance of the left kidney with regular corticomedullary differentiation and size. Color-Doppler sonography and Doppler spectrum of an intrarenal artery demonstrate a normal waveform and a normal early systolic compliance peak without abnormal findings.

Atypical relations between metabolic control and morphologic damage can exist. The interesting nosological entity of "diabetic nephropathy without diabetes" means that typical diabetic kidney lesions develop in patients without overt diabetes [157-159]. In about half of the reported cases, signs of glucose intolerance are found only after careful analysis. This finding confirms the importance of the interplay between genetic background and metabolic control, beyond a simplistic interpretation of diabetic nephropathy as a disease strictly related to sustained hyperglycemia [158-159].

6. Diabetic nephropathy in type 2 diabetes: diabetes as a disease or as a comorbid condition?

The morphology of the renal lesions in type 2 diabetes is considered to be almost indistinguishable from that in type 1 diabetes. In contrast, the natural history of kidney disease frequently differs. This discrepancy is mainly due to the shorter interval between diagnosis and overt renal disease in type 2 diabetes, an occurrence that was initially and simplistically explained by the subtle and non-symptomatic onset of type 2 diabetes. This has been increasingly described in young type 2 diabetics, where the genetic background may play an important role [160-167].

Typically in the elderly, the clinical picture of a diabetic patient may be dominated by diabetes and its complications. Alternatively, hypertension, lipid derangements, and obesity may progress into a dysmetabolic syndrome (the "metabolic syndrome" par excellence), in which diabetes is just one component. This concept is known as the "inactivity paradigm". Therein, diabetes is regarded as a "comorbid factor" in a disease that is dominated by obesity and vasculopathy. In this concept, the primary kidney diseases are renal vascular and nephroangiosclerotic diseases [168-171].

A few studies have addressed the following question in dialysis patients: is there any difference between diabetes as a comorbid condition (possibly with onset during dialysis) and diabetes as the cause of kidney disease? While smaller studies suggested that there is no difference, a recent large study based on the ERA-EDTA Registry found that mortality is higher in patients with diabetes as the primary renal disease compared to those with diabetes as a co-morbid condition. This finding suggests that survival is affected by the extent to which diabetes has caused organ damage, mainly within the cardiovascular system [172-174].

7. Progressive renal decline and non-albuminuric diabetic nephropathy: a new paradigm in type 1 diabetes

According to the classic concept, diabetic nephropathy is a disease marked by an increase in proteinuria during its progression. However, this concept has recently been challenged by the description of non-proteinuric (or non-nephrotic proteinuric) kidney disease in diabetic patients [71, 73, 41, 175-180]. The term "pauciproteinuria" has been implemented to describe these cases [179]. More than a decade ago, this clinical picture was described as a facet of the cardiovascular impairment in diabetic patients. The reasons for the change in recognition of this disease were due to the detection of various lesions and the establishment of alternative diagnoses that include the full spectrum of vascular nephropathies, including interstitial (and/or drug-induced) diseases, pyelonephritis, obstructive nephropathies, recurrent bouts of acute kidney injury, and change in the natural history of the disease due to improved therapies [176-181].

In some reports by our group, we described kidney disease in diabetic patients not characterized by proteinuria. These cases encompassed various conditions including metabolic derangements, genetic syndromes, and "primary" nephroangiosclerosis [182-185]. In a recent series of pregnant patients with "severe" kidney disease and type 1 diabetes, median proteinuria was 1.6 g/day at the start of pregnancy or at referral. While proteinuria ranged from 0.1 to 6.3 g/day, the lower level was observed in a diabetic patient with biopsy-proven diabetic nephropathy involving almost 50% of glomeruli. The median GFR was 67 ml/min. Retinopathy was present in all patients and clinical neuropathy in half of them [186]. This confirms that signs of diabetic nephropathy, as determined by kidney biopsy, can co-exist with minor clinical signs.

The changing pattern of nephropathy alongside the improvement in care suggests a similarity with AIDS-related nephropathies that increasingly present with less immune complex-mediated glomerular disease and more non-collapsing focal-segmental glomerulopathy. Currently these changing patterns cannot be explained; they are likely multifactorial. Antiretroviral therapies, renin-angiotensin-aldosterone system (RAAS) antagonists, earlier nephrology referral, and generally improved medical care may all play a role [187-188].

8. The changing pattern of glomerulosclerosis: a lesion rather than a disease

Our knowledge of several kidney diseases has improved and our treatment approaches are continuously being modified accordingly. This is also true for focal segmental glomerulosclerosis (FSGS); its disease profile consistently overlaps with diabetic nephropathy [189]. While skilled pa-

thologists are able to distinguish between primary and secondary FSGS, the differences are not always clear. FSGS is one of the most frequently reported "non-diabetic" lesions in a recent study of a series of diabetic patients who underwent kidney biopsy [149, 190-191]. Curiously, this condition has not been reported previously, suggesting that FSGS and global glomerulosclerosis in diabetes may appear similarly, at least in some cases. In a series of such cases, patients that were classified as having diabetic nephropathy without retinopathy, were diagnosed with diffuse glomerulosclerosis, a non-nodular form of diabetic nephropathy [192].

Traditionally, secondary FSGS is regarded as a disease that is mediated hemodynamically. It is considered to be the result of a vast array of events, including drug effects, infections, and genetic mutations. Obesity has frequently been associated with this disease. Indeed, focal segmental glomerulosclerosis is the most common renal lesion observed in obese patients [189, 193-197]. As obese type 2 diabetic patients form a large subset of the entire population of diabetic subjects, diabetes and kidney disease may be associated with obesity as a comorbidity or, on the contrary, obesity-related glomerulopathy may have diabetes as a comorbid condition [190, 198, 199].

The search for a common pathway, which has already been attempted in FSGS, may be extended to some of the general glomerulosclerotic lesions in diabetes, and to their relationship with the focal lesions of FSGS. This consideration further highlights the discrepancy between metabolic demand and nephron mass.

9. Incidental association of glomerular diseases and diabetes: just a question of probability?

It has been difficult to find a cause-effect relationship or a common pathogenic link between the presence of diabetes and the prevalence of glomerular diseases, in particular membranous nephropathy [200-205]. The finding of (porcine) insulin deposits in the glomeruli in the context of membranous nephropathy may be regarded as evidence for such a link. However, there is also evidence for the lack of a direct relationship between diabetes and other glomerular diseases, namely the fact that the patterns of the biopsy-proven glomerular diseases vary over the world, and mainly reflect the most common glomerular diseases in the resident population [53, 124, 177-180, 190-192].

The assumption of a cause-effect relationship is supported by the simultaneously increasing prevalence of both diabetes and chronic kidney disease. Each of these diseases presently affects more than 10% of the population in high-income countries, with sharply rising incidences worldwide. The increased combined appearance of diabetes and kidney disease may be due to the rising attention for early diagnosis in diabetic patients, and concomitant early diagnosis of otherwise overlooked diseases such as CKD [206-212].

10. Impairment of kidney function in diabetic patients: metabolic aspects beyond GFR

While kidney damage is often defined by the presence of albuminuria and/or impaired GFR, several recent studies found early endocrine derangements in diabetic kidneys compared with non-diabetic kidney [212-214]. Indeed, erythropoietin synthesis has been reported to decline earlier in the diabetic than in non-diabetic CKD. This is an important finding since erythropoietin deficiency may enhance the vascular anoxic lesions in glomerulopathy or retinopathy [215-218].

Early derangements in the vitamin D-PTH axis have also been described. Vitamin D receptor polymorphisms have been implicated in the pathogenesis of diabetes and its complications [219-220]. Hyporeninemic hypoaldosteronism is another impairment that has been described in diabetic patients. The occurrence of this impairment may explain the disproportion between hyperkalemia and the rise in serum creatinine and/or in the absence of ACE-inhibitor and/or angiotensin receptors inhibitors [221-222].

11. Other chronic kidney diseases associated with diabetes: vascular kidney disease, renal infarction, and cholesterol emboli syndrome

The kidney can be regarded as an "atlas" of blood vessels of different size and specialization (filtration, concentration, higher or lower porosity). Diabetes may be described as a systemic metabolic disease with micro- and macrovascular complications. It is thus no surprise that all the vascular lesions that can occur in kidney diseases are also described in diabetes patients.

Atherosclerotic stenosis of the main renal arteries and their branches are a common and fre-

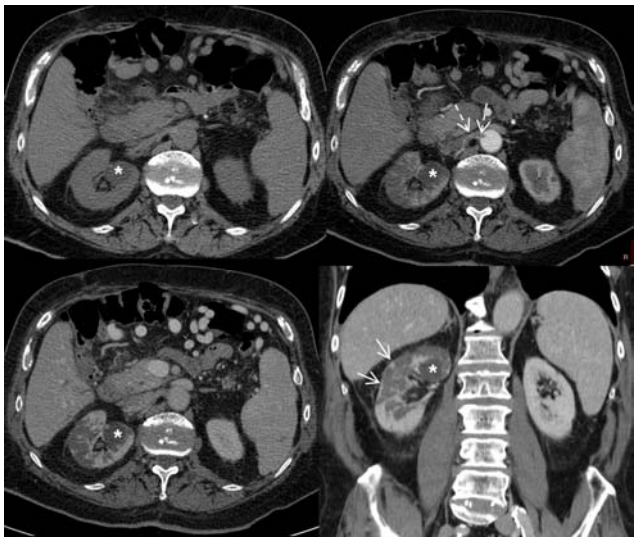

Figure 5. Unenhanced and multiphase-enhanced helical computed tomography in a 78 years old man with type 2 diabetes mellitus and renal infarction. The pre-contrast scan shows homogeneous attenuation of the kidneys. The corticomedullary arterial phase and the nephrographic phase demonstrate multiple round- and wedge-shaped focal areas of decreased enhancement in the right kidney with loss of corticomedullary differentiation due to multiple infarctions. The arterial phase demonstrates a thrombus of the right renal artery as a filling defect extending from the ostium to the proximal segment of the main renal artery (dotted arrows). Coronal reformation of the nephrographic phase detects a thin rim of capsular enhancement (arrows) known as the "cortical rim sign", which suggests a diagnosis of renal infarction. A fluid cortical cyst is visible in the upper part of the right kidney (asterisks).

quently overlooked component of severe diffuse atherosclerosis in diabetic and non-diabetic patients. Renal artery stenosis can be observed in about one third of cases with concomitant hypertension and/or kidney function impairment [224-226]. However, the old tenet that the presence of renal artery stenosis may be revealed by unstable blood pressure that requires more than two drugs for control or by severe hypertensive crises is unsustainable. Most of the patients with renal artery stenosis do not have clinical features specific enough to differentiate them from other hypertension and vasculopathy patients.

The proposed scores to identify patients with renal artery stenosis are indeed based on the presence of diffuse vascular disease, hypertension, and high serum creatinine [227-228]. However, diagnosis is complicated by frequent multiorgan involvement and the lack of information regarding the degree of revascularization. Whilst diagnosis is only the first step towards a tailored treatment, it is necessary to address the specific conditions in any single patient [229]. Furthermore, an acute increase in serum creatinine after intake of ACE inhibitors or angiotensin receptor blockers (ARBs) may be observed in the presence of microvascular disease. However, if a diabetic nephropathy patient has been on long-term therapy with ACE inhibitors or ARBs, an acute increase is unlikely, and a gradual increase may be overlooked because of a well-known underlying kidney disease [230-232].

In our experience, the occurrence of acute kidney injury (AKI) in the context of dehydration or overzealous diuretic use may be a complementary element in the diagnosis of renal artery stenosis. We believe that a systematic assessment of the renal arteries should be performed in all diabetic and vasculopathic patients. Also, the use of ACE inhibitors and ARBs should be limited, and only considered in selected patients with severe proteinuria, as these drugs *per se* represent a risk of inducing AKI [233-234].

Renal infarction is a rare complication that frequently involves stenosis of the large arterial vessels. It occurs usually within the intraparenchymal branches. This should be considered when a diabetic patient develops a clinical picture that is at first glance indistinguishable from that of acute pyelonephritis (described in the next paragraph). The main clues for acute infarction versus acute pyelonephritis derived from imaging investigation include:

- Absence of perinephric involvement and renal swelling
- Absence of spatial relationship with the calyces
- Sharper differentiation of the lesion (if assessed at presentation)

The biochemical picture of renal infarction may be identical to that of pyelonephritis, but specific features include the slower decrease of C-reactive protein as a response to antibiotic therapy and the higher levels of lactate dehydrogenase (LDH), especially at first presentation (**Figure 5**) [235-237].

Involvement of medium-sized arteries in the kidney parenchyma has been extensively described as a frequent occurrence in diabetic kidney disease (e.g. in the recent Tervaert classification), and it has recently been associated with the "non-

proteinuric" or "pauciproteinuric" pattern in diabetic kidney disease. The extensive involvement of the renal vasculature may explain the frequently observed stepwise increase in serum creatinine, which is less common in the "classic" forms of proteinuric diabetic nephropathy [109].

Small and medium-sized vessels are also a target of the cholesterol emboli syndrome, an emerging clinical condition that is frequently overlooked because of its clinical mimicry. Typical cases are linked to vascular manipulations or changes in anticoagulant-antiaggregant therapy, and may present with livedo, vasculitis-like skin lesions, and progressive renal impairment weeks or months after the manipulation or therapeutic change. Skin and kidney are frequently involved, but any organ can be affected. The so called "spontaneous" lesion is insidious and difficult to diagnose. It is usually linked to the presence of an ulcerated plaque and a rapid decrease in kidney function in the context of diffuse atherosclerosis [238-243].

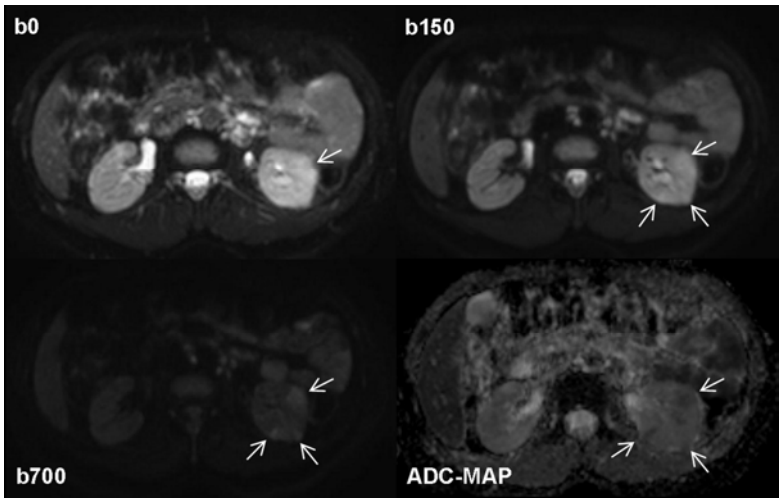

Figure 6. Computed tomography (CT) and diffusion-weighted magnetic resonance imaging (MRI) in a 60 years old type 2 diabetes patient who presented with bilateral acute flank pain at the emergency department. Unenhanced helical CT scan of the abdomen (upper image) shows homogeneous attenuation of both kidneys, normally shaped and sized, without calcifications or stones. The appearance of fat around the kidneys is normal and homogeneous with no stranding or fluid collections throughout the perinephric space or within the peri-renal fascia. The apparent diffusion coefficient map obtained from diffusion-weighted MRI (lower image) at the same day as CT examination demonstrates multiple round- and wedge-shaped areas of hypo-intensity in the cortex of both kidneys (arrows), with restricted diffusion to the movement of water molecules (mean apparent diffusion coefficient (ADC) value of 1.38 x $10^{-3}mm^2s^{-1}$), which suggests foci of bilateral acute pyelonephritis.

12. Upper urinary tract infection as another acute and chronic kidney disease associated with diabetes

12.1 Upper urinary tract infections

The reason why urinary tract infections are frequent in diabetic patients has long been a matter of speculation. Glycosuria was initially considered a relevant factor as it constitutes a basis for bacterial growth. However, the risk of urinary tract infection is not higher in patients with isolated euglycemic glycosuria, thus suggesting a more complex relationship between host and local risk factors [244]. In any case, diabetic patients are at higher risk for severe parenchymal lesions, including unusual complicated urinary tract infections such as emphysematous pyelonephritis, malakoplakia, and "renal carbuncle" [245-250].

12.2. Acute pyelonephritis and upper urinary tract infection

Acute pyelonephritis in diabetic patients is multifactorial and frequently severe, with a high incidence of abscessed lesions (**Figures 6** and **7**). Based on the experience of our group, diabetic patients presenting with a clinical picture of acute urinary tract infection should undergo a second-line imaging test (computed tomography (CT) scan with contrast media, or magnetic resonance imaging (MRI) with or without gadolinium). Long-term intravenous therapy is probably needed to avoid kidney scars [251-254]. The condition may also include subtle defects in the immunologic response, mainly involving phagocytosis. It may thus be regarded as a comorbidity of diabetes, and seems to be closely correlated to the quality of glucose control [255].

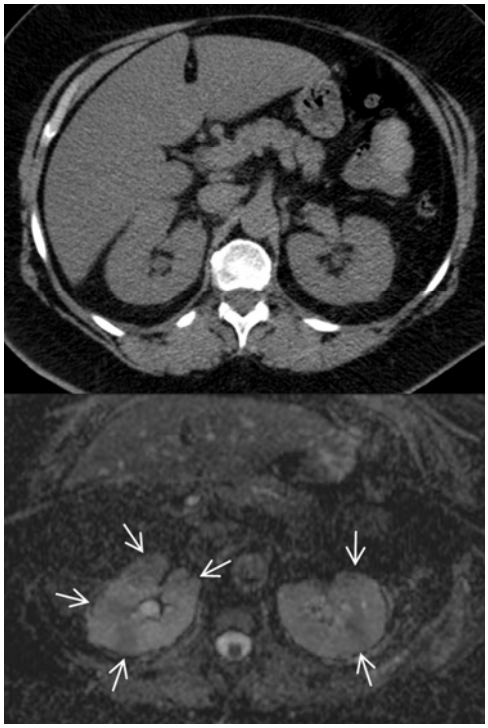

Figure 7. Diffusion-weighted MRI in a 38 years old patient with type 1 diabetes and acute bacterial pyelonephritis in the left kidney. Native diffusion-weighted images obtained at b values of 0 and 150 sec/mm^2 show some cortical wedge-shaped areas of faint hyper-intensity that are well detectable. The areas persist at the higher b value of 700 sec/mm^2 (arrows) suggesting reduced diffusion due to inflammatory edema and acute pyelonephritis. This finding is confirmed by the apparent diffusion coefficient map obtained from b values of 150 and 700 sec/mm^2, a procedure carried out to exclude vascular components detected by the MRI signal, which shows areas of low signal intensity (arrows; mean ADC value of 1.25 x 10^{-3}mm^{2}s^{-1}) and healthy tissue for comparison reasons to see inflammatory parenchymal changes.

12.3 Adverse environmental and drug-disease effects and acute or chronic renal impairment

We are living in a polluted world. It is therefore not surprising that most patients are at an increased risk of renal toxicity. The risk is linked to the complex polypharmacy that is usually prescribed in patients with diabetes and advanced CKD [256-258]. A recent review summarized potential drug-disease interactions between drugs recommended in the guideline for type 2 diabetes and 11 comorbid conditions. While 32 potentially serious drug-disease interactions have been reported, the adverse interactions were most common in type 2 diabetes patients with chronic kidney disease (27/32) [258].

Adverse effects of drugs on the kidney are frequent; they can cause acute or chronic impairment of renal function, and their effect may be hemodynamic, toxic, or immunoallergic [259-262]. While virtually all drugs may cause one or more forms of renal impairment, baseline risks are enhanced by the presence of kidney disease, and increased in proportion to the number of prescribed drugs [263-264].

Many toxicity-related renal damages are direct and have clear symptoms. Therefore, they are rapidly evident, even in the absence of the classical hallmarks of skin rash, fever, and eosinophilia. They include the previously called "immunoallergic" acute tubulo-interstitial nephritis (as described for antibiotics, acetaminophen, non-steroidal anti-inflammatory drugs, and allopurinol) and hemodynamic adverse effects (e.g. those caused by ACE-inhibitors and ARBs). However, one of the most alarming aspects of renal toxicity is that chronic damage may escape identification for a long time [265-269].

While a detailed discussion of these effects is beyond the scope of this review, it is worth noting that many drugs involved in biopsy-proven interstitial nephritis are commonly prescribed in elderly and diabetic patients (including proton pump inhibitors, allopurinol, anti COX-2, and antibiotics) [265-269].

Another important issue regards contrast media: the association between diabetes and risk for contrast media-induced nephropathy has already been described in the '80s, in particular in patients treated with metformin. These patients are at a higher risk of lactic acidosis. More recent data suggest that diabetic patients with proteinuria should receive particular attention as they are sensitive to kidney damage by contrast media. Also, high pre-procedural glucose blood levels are important in the prediction of adverse effects [270-276].

The actual incidence of these potentially severe diseases is not known, but they probably contribute significantly to the interstitial diseases observed as "non-proteinuric" renal diseases in diabetic patients.

Finally, we should not forget that the kidney has further crucial metabolic, endocrine, and enzymatic properties, including the previously mentioned role in erythropoiesis, vitamin D metabolism and renin-angiotensin axis, glycogen synthe-

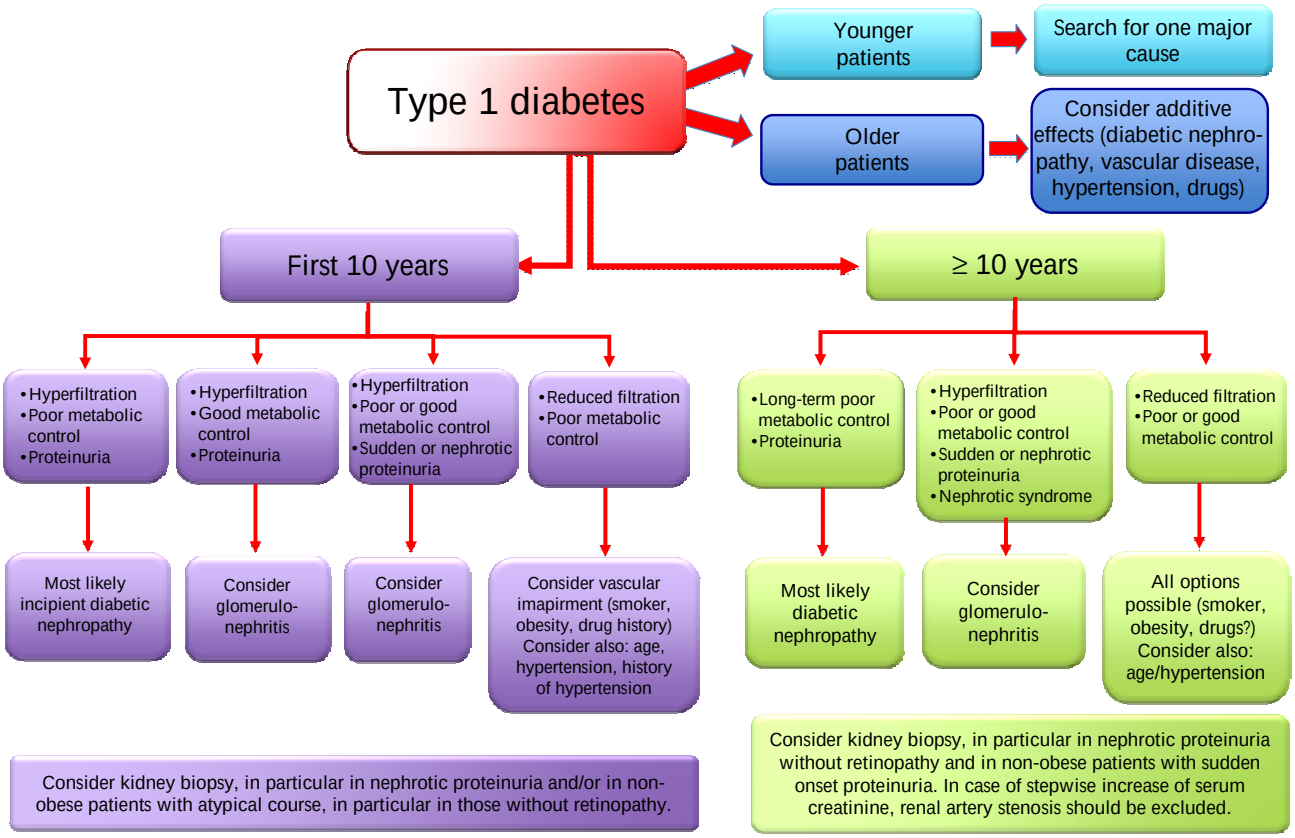

Figure 8. Schematic flow-chart for the diagnosis of kidney disease in type 1 diabetes.

sis, and renalase or insulinase. The pathology-function relationship is presumably important, but its clinical role is not completely understood, and will surely be a matter of future research.

13. Conclusions

The old term "diabetic kidney" was recently re-proposed to encompass the various lesions that characterize the multifaceted, protean kidney damage in diabetic patients. The distribution of nodular and diffuse forms of glomerular lesions in diabetes patients has changed over time. While nodular glomerulosclerosis may be an indication of poorly controlled diabetes, and therefore improvement with better control is possible, both forms are characterized by an increase in proteinuria combined with a decrease in renal function.

However, the old tenet that proteinuria identifies "diabetic nephropathy" may no longer be true, or should be limited to glomerular lesions. The improvement in diabetic control may have reduced such typical lesions and may have revealed an increase in other types of renal damage, mainly vascular and interstitial types that typically present with little proteinuria. This has heralded the new trend of discussing the "new paradigm" of non-proteinuric kidney disease.

However, from a pathophysiological point of view, it is not surprising that all main kidney structures may be involved in kidney disease. Why? In a medicated society, in which the kidney is the target of drug and environmental toxicity, the presence of underlying renal damage through diabetes-related micro- and macrovascular kidney damage sets the stage for full-blown kidney disease and acute drug-induced kidney injury. In addition, impairment in the phagocytic response may be another factor causing the onset of severe and unusual forms of renal damage, including acute and chronic pyelonephritis. Therefore, a mere screening for albuminuria, although useful for detecting the "glomerular" forms of diabetic nephropathy, is not sufficient to detect all the potential

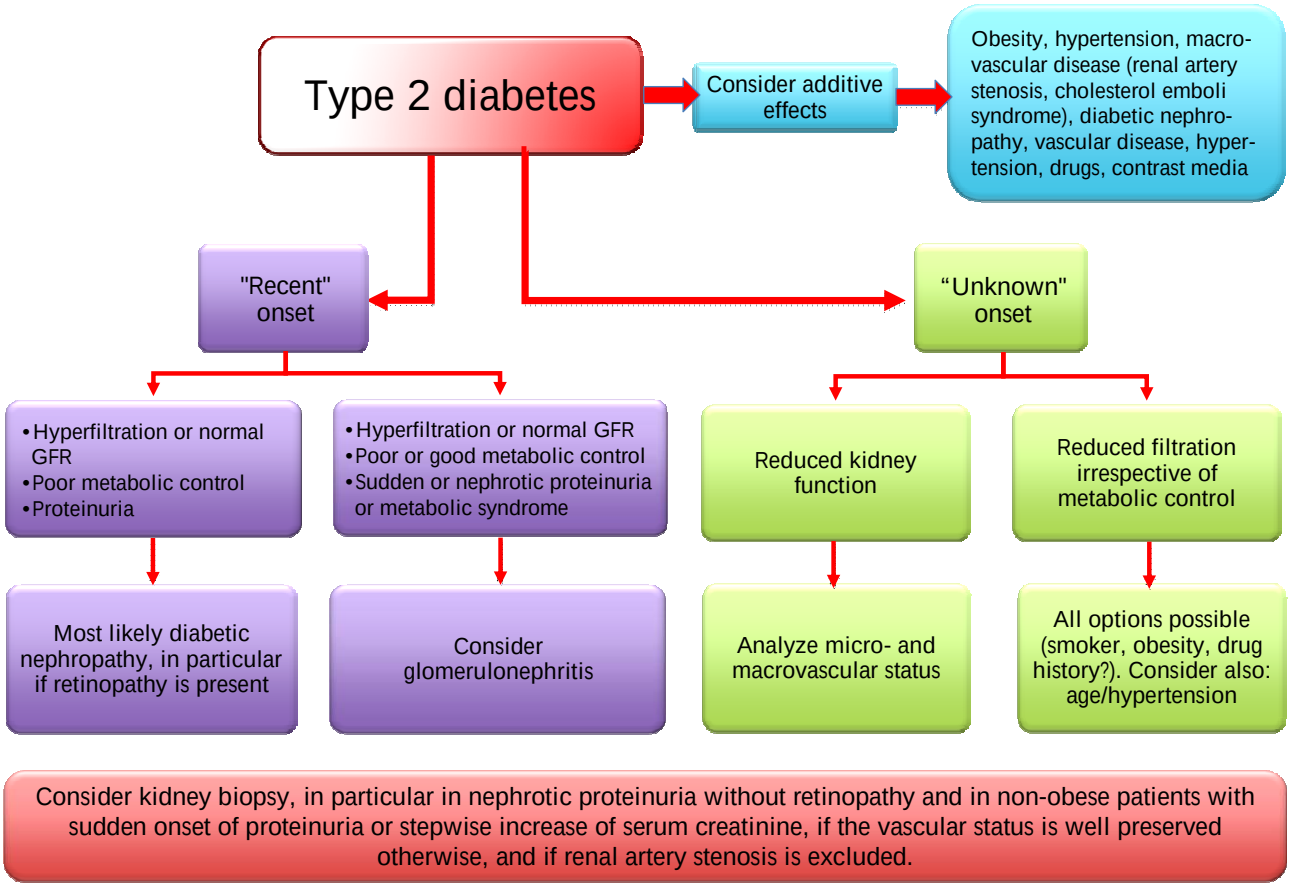

Figure 9. Schematic flow-chart for the diagnosis of kidney disease in type 2 diabetes.

nephropathies in diabetics. Further investigation needs to be carried out.

Diabetes is a risk factor for all forms of kidney disease. Diabetes patients are more prone to develop all kinds of clinical renal damage, and may suffer more severely from rapid progression. Kidney disease in diabetic patients should be identified by the same combination of biochemical, clinical, and imaging tests, as employed in the non-diabetic population. However, investigation methods including contrast medium can cause renal damage. Therefore, these methods should be used carefully in this fragile subset of patients who may have already lost their "renal reserve" (**Figures 8** and **9**).

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