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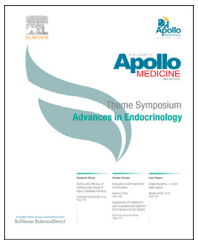

Review Article

Diabetes and kidney disease

*Umesh Lingaraj**, *Chandrashekar Annamalai*, *Hemachandar Radhakrishnan*

Department of Nephrology, Apollo Hospitals, Bangalore, India

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ABSTRACT

Diabetes mellitus is a worldwide epidemic. Its prevalence is on a steep rise and is more pronounced in India making it the 'diabetes capital of the world'. There is also a parallel increase in the prevalence of diabetic nephropathy and is now the single most common cause of end-stage kidney disease leading to significant morbidity and mortality as well as accounts for a tremendous burden on the health care costs. It is also shown that the presence of diabetes increases the risk and progression of non-diabetic kidney disease. Currently available therapies aim at optimizing glycemic control and systemic blood pressure involving the blockade of the renin-angiotensin-aldosterone system although, have shown beneficial effect, the reduction in progression of the disease has been modest at best. This article reviews current treatment options and provides an overview of novel therapeutic agents that hold great potential for the treatment of diabetic kidney disease as well as to emphasize upon the importance of considering the possibility of a potentially reversible non-diabetic renal disease in diabetic patients with kidney involvement.

1. Introduction

Diabetes mellitus is a worldwide epidemic. Its prevalence is on a steep rise and is more pronounced in India[1,2] making it the 'diabetes capital of the world'. Up to 40% of patients with diabetes will develop some form of kidney damage.[3] Diabetes has become the most common single cause of end-stage renal disease (ESRD) worldwide and is associated with increased cardiovascular mortality. This is due to the facts that: 1) diabetes, particularly type 2, is increasing in prevalence; 2) diabetes patients now live longer; and 3) patients with diabetic ESRD are now being accepted for treatment in ESRD programs where formerly they had been excluded.[4] Recent studies have now demonstrated that the onset and course of diabetic nephropathy can be ameliorated to a very significant degree by several interventions, but these interventions have their greatest impact if instituted at a point very early in the course of the development of this complication. This article reviews the clinical features and current strategies in the management of diabetic nephropathy and also emphasizes the importance of recognizing potentially reversible non-diabetic renal disease in patients with atypical clinical features.

2. Magnitude of the problem

The incidence of diabetes is raising rapidly worldwide. The worldwide prevalence of diabetes has been predicted to reach 366 million by 2030, up from 171 million in 2000.[5] In India, the overall crude prevalence of diabetes using WHO criteria as per the Chennai Urban Rural Epidemiology Study (CURES) is 15.5% while that of IGT is 10.6%.[6] Among the diabetics in urban areas, the prevalence of overt diabetic nephropathy and

* *Corresponding author.*
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microalbuminuria has been found to be 2.2% and 26.9%, respectively.[6]

3. Natural history of diabetic nephropathy

About 20–30% of patients with type 1 or type 2 diabetes develop evidence of nephropathy.[4] Diabetic nephropathy has been didactically categorized into stages based on the values of urinary albumin excretion (UAE): microalbuminuria and macroalbuminuria.

The earliest clinical evidence of nephropathy is the appearance of low but abnormal levels (≥30 mg/day or 20 μg/min) of albumin in the urine, referred to as microalbuminuria or incipient nephropathy. Without specific interventions, ~80% of subjects with type 1 diabetes who develop sustained microalbuminuria have their urinary albumin excretion increase at a rate of ~10–20% per year to the stage of overt nephropathy or clinical albuminuria (≥300 mg/24 h or ≥200 μg/min) over a period of 10–15 years, with hypertension also developing along the way. Once overt nephropathy occurs, without specific interventions, the glomerular filtration rate (GFR) gradually falls over a period of several years at a rate that is highly variable from individual to individual (2–20 ml/min/year). End-stage renal disease develops in 50% of type 1 diabetic individuals with overt nephropathy within 10 years and in >75% by 20 years.[4]

A higher proportion of individuals with type 2 diabetes are found to have microalbuminuria and overt nephropathy shortly after the diagnosis of their diabetes, because diabetes is actually present for many years before the diagnosis is made without specific interventions, 20–40% of type 2 diabetic patients with microalbuminuria progress to overt nephropathy, but by 20 years after onset of overt nephropathy, only ~20% will have progressed to ESRD. Once the GFR begins to fall, the rates of fall in GFR are again highly variable from one individual to another, but overall, they may not be substantially different between patients with type 1 diabetes and patients with type 2 diabetes. However, the greater risk of dying from associated coronary artery disease in the older population with type 2 diabetes may prevent many with earlier stages of nephropathy from progressing to ESRD.

4. Diagnosis of diabetic kidney disease

In most patients with diabetes, CKD should be attributable to diabetes if either macroalbuminuria is present or microalbuminuria is present in the presence of diabetic retinopathy, or in type 1 diabetes of at least 10 years' duration in the absence of clinical or laboratory evidence of other kidney or renal tract disease.[7] Other cause(s) of CKD should be considered in the presence of any of the following circumstances[7]:

- Absence of diabetic retinopathy;
- Low or rapidly decreasing GFR;
- Rapidly increasing proteinuria or nephrotic syndrome;
- Refractory hypertension;
- Presence of active urinary sediment;
- Signs or symptoms of other systemic disease; or
- >30% reduction in GFR within 2–3 months after initiation of an ACE inhibitor or ARB.

Hence diabetic nephropathy is a clinical diagnosis. In a recent retrospective study, Biesenbach et al reported a sensitivity of 95% for the clinical diagnosis of diabetic nephropathy and a specificity of 78%. According to them, renal biopsy is not required in the majority of type 2 diabetic patients who exhibit all criteria for clinical diagnosis.[8]

5. Screening for albuminuria

A test for the presence of microalbuminuria should be performed at diagnosis in patients with type 2 diabetes. Microalbuminuria rarely occurs with short duration of type 1 diabetes; therefore, screening in individuals with type 1 diabetes should begin after 5 years' disease duration. Because of the difficulty in precise dating of the onset of type 2 diabetes, such screening should begin at the time of diagnosis. After the initial screening and in the absence of previously demonstrated microalbuminuria, a test for the presence of microalbuminuria should be performed annually.

Screening for microalbuminuria can be performed by two methods either measurement of the albumin-to-creatinine ratio in a random spot collection or a 24-h urine collection for estimation of albumin with creatinine, allowing the simultaneous measurement of creatinine clearance. The first method is often found to be the easiest to carry out, generally provides accurate information, and is therefore preferred; first-void or other morning collections are best because of the known diurnal variation in albumin excretion. Because of variability in urinary albumin excretion, two of three specimens collected within a 3- to 6-month period should be abnormal before considering a patient to have crossed one of these diagnostic thresholds. Exercise within 24 h, infection, fever, congestive heart failure, marked hyperglycemia, marked hypertension, pyuria, and hematuria may elevate urinary albumin excretion over baseline values (Table 1).

Table 1 – Definitions of abnormalities in albumin excretion.[9]

Category	Spot collection (μg/mg creatinine)	24-h collection (mg/24 h)	Timed collection (μg/min)
Normal	<30	<30	<20
Microalbuminuria	30–299	30–299	20–199
Clinical albuminuria	≥300	≥300	≥200

The role of annual microalbuminuria assessment is less clear after diagnosis of microalbuminuria and institution of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy and blood pressure control. Many experts recommend continued surveillance to assess both response to therapy and progression of disease.

Higher levels of albuminuria even within normal range (concentrations < 30 mg/day) predict cardiovascular events. Hence, it has been suggested to abandon the concept of 'microalbuminuria' and to treat urine albumin concentration as a continuous variable as, for instance, serum cholesterol.[10] Microalbuminuria is a strong predictor of total and cardiovascular mortality and cardiovascular morbidity in diabetic patients.[11]

Serum creatinine is measured in all patients with diabetes and the GFR is estimated from a creatinine-based equation such as the Modification of Diet in Renal Disease (MDRD) equation.[12] The recently proposed Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[13] provides a more accurate estimate of GFR from serum creatinine than the MDRD equation, especially at higher GFR values.[14]

6. Pathophysiology

Diabetic nephropathy results from a complex interplay of genetic, metabolic and hemodynamic factors. Several putative promoters of progression in kidney dysfunction have been studied in patients with diabetes who have nephropathy. Systemic hypertension, intraglomerular hypertension, poor glycemic control, proteinuria, impaired renin-angiotensin-aldosterone system, obesity, dietary protein intake, smoking, dyslipidemia, and ACE ID polymorphism were few among them known to promote the progression of diabetic nephropathy.[15–20]

The constellation of the renal structural lesions occurring in diabetes is unique, although each of these lesions can be individually observed in other renal disorders. GBM thickening, the first measurable change, has been detected as early as 1.5–2.5 years after the onset of T1DM.[21,22] Thickening of tubular basement membrane (TBM) closely parallels that of GBM thickening. Mesangial expansion, predominantly due to an increase in mesangial matrix, develops later although an increase in the matrix component of the mesangium can be detected as early as 5–7 years after the onset of diabetes.[23–25] Thereafter, these structural changes do not necessarily develop at the same rate in the individual patients.[26]

Diffuse mesangial expansion, commonly termed diffuse diabetic glomerulosclerosis, can be associated with nodular lesions consisting of areas of marked mesangial expansion forming large round fibrillar mesangial zones with palisading of mesangial nuclei around the periphery of the nodule and compression of the associated glomerular capillaries (Kimmelstiel–Wilson nodules). Afferent and efferent arteriolar hyalinosis may be present within a few years after diabetes onset.

Marked renal extracellular basement membrane accumulation resulting in extreme mesangial expansion and GBM thickening are present in the vast majority of T1DM patients who develop overt diabetic nephropathy (DN) manifesting as proteinuria, hypertension, and declining GFR. Ultimately, focal and global glomerulosclerosis, tubular atrophy, interstitial expansion and Glomerular-Tubular Junction Abnormalities (GTJA) facilitate this downward spiral.[27] Tubulointerstitial disease may be more important in the progression from moderate renal insufficiency to end-stage renal disease (ESRD).[28]

7. Treatment

The major therapeutic interventions that have been investigated include control of blood glucose, antihypertensive treatment, lipid-lowering therapy, restriction of dietary proteins, smoking cessation, and renin-angiotensin-aldosterone system (RAAS) inhibition. The impact of these treatment modalities on progression from normoalbuminuria to microalbuminuria (primary prevention), microalbuminuria to diabetic nephropathy (secondary prevention), and diabetic nephropathy to ESRD (tertiary prevention) is discussed below.

7.1. *Glycemic control*

In the Diabetes Control and Complications Trial (DCCT), intensive therapy reduced the occurrence of microalbuminuria by 39%, and that of macroalbuminuria by 54% in type 1 diabetes patients.[29] In Japanese type 2 diabetic patients a beneficial impact of strict glycemic control on progression of normoalbuminuria to microalbuminuria and macroalbuminuria was demonstrated in a small study with a design similar to that of the DCCT.[30] Results of this study have been confirmed and extended by data from the UK Prospective Diabetes Study (UKPDS) documenting a progressive beneficial effect of intensive metabolic control on the development of microalbuminuria and overt proteinuria,[31] and a 10-year poststudy follow-up demonstrated a long-lasting beneficial effect.[32]

The beneficial effect was recently confirmed in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) study, in which 11,140 patients with type 2 diabetes were followed for a median of 5 years and a 21% reduction (95% CI = 7–34%) in development of nephropathy was seen in patients randomly assigned to strict glycemic control.[33]

However, it was further observed that very strict HbA1c control did not significantly reduce the micro or macrovascular complications in the Veteran Affairs Diabetes Trial (VADT).[34] ACCORD trial too investigated the effect of lowering HbA1c level below 6% and had to be prematurely terminated after a median follow-up of 3.4 years because of excess mortality in the intensive therapy group.[35]

The American Diabetes Association (ADA) and the National Kidney Foundation (NKF) both recommend a target HbA1c of 7.0% in patients with diabetes, irrespective of the presence of CKD.[36] In contrast to the benefit of aggressive therapy in patients with microalbuminuria, however the role of intensive glucose control in patients with overt proteinuria is minimal or of no benefit.

7.2. Blood pressure control

High blood pressure accelerates the kidney deterioration and optimal hypertension control has a beneficial effect on kidney function as shown by the UKPDS study,[37] the Hypertension Optimal Treatment trial,[38] and the recent ADVANCE study.[39] Based on these studies NKF-KDOQI has recommended that target blood pressure in diabetes and CKD stages 1–4 should be <130/80 mmHg.[36]

In the International Verapamil SR-Trandolapril study[40] the risk of all-cause death, nonfatal myocardial infarction or nonfatal stroke was increased with a diastolic blood pressure lower than 70 mmHg. Similar results were observed in the ACCORD trial at systolic blood pressure below 120 mmHg[41] and was rather associated with a higher incidence of serious adverse events with intensive antihypertensive therapy. These data does not support lowering the current blood pressure goal of 130/80 mmHg.

7.3. RAAS blockade

In addition to antihypertensive effect, RAAS inhibitors have additional renoprotective effects that have been confirmed in multiple trials. The Renin Angiotensin System Study (RASS) in type 1 diabetic patients who were normotensive and normoalbuminuric did not find any benefit of RAS blockade on the progression of albumin excretion rate.[42] The DIRECT study did not show any significant effect on the incidence of microalbuminuria.[43] The Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) demonstrated that use of an ACE inhibitor, alone or in combination with a calcium channel blocker, decreases the incidence of microalbuminuria in hypertensive type 2 diabetic patients with normoalbuminuria.[44]

In the recent ADVANCE study, which included type 2 diabetic patients with or without hypertension, the fixed combination of perindopril and the diuretic indapamide also reduced blood pressure, and the development of new-onset microalbuminuria was reduced by 21%.[39] In conclusion, RAS blockade has been effective in reducing the frequency of development of microalbuminuria in hypertensive normoalbuminuric patients, whereas the effect has not been significant in normotensive patients.

The IRMA 2 study evaluated the renoprotective effect of the angiotensin II receptor antagonist irbesartan in hypertensive patients with type 2 diabetes and microalbuminuria demonstrated that irbesartan is renoprotective independent of its blood pressure-lowering effect in patients with type 2 diabetes and microalbuminuria.[45]

In 1993, the Captopril Collaborative Study Group demonstrated a significant reduction (48%; 95% CI = 16–69%) in the risk of a doubling of serum creatinine concentrations in patients with type 1 diabetes and nephropathy who received captopril.[46] Two large multinational double blind, randomized, placebo-controlled trials of ARBs—the RENAAL study[47] and the Irbesartan Diabetic Nephropathy Trial (IDNT)[48]—were carried out in comparable populations of hypertensive patients with type 2 diabetes, proteinuria, and elevated serum creatinine levels. In both trials, the primary outcome (composite of a doubling of the baseline serum creatinine concentration, ESRD, or death) was significantly reduced in patients treated with ARBs. Based on these three outcome trials of ARBs, the American Diabetes Association now states, "In patients with type 2 diabetes, hypertension, macroalbuminuria and renal insufficiency (serum creatinine >1.5 mg/dl), ARBs have been shown to delay the progression of nephropathy."[49]

The American Diabetes Association now states the following: "In patients with hypertension and any degree of albuminuria ACE inhibitors have been shown to delay the progression of nephropathy. In patients with type 2 diabetes, hypertension and microalbuminuria, both ACE inhibitors and ARBs have been shown to delay the progression to macroalbuminuria. In patients with type 2 diabetes, hypertension, macroalbuminuria and renal insufficiency (serum creatinine >1.5 mg/dl), ARBs have been shown to delay the progression of nephropathy".[49]

7.4. Dual RAAS blockade

In the ONTARGET study, 25,620 patients with atherosclerotic disease or diabetes (38% with diabetes) who had end-organ damage were randomly assigned to treatment with an ACE inhibitor, angiotensin receptor blocker (ARB), or both and were followed for a median of 56 months. Although the combination treatment reduced the increase in urinary albumin excretion rate (AER), the number of events for the composite primary outcome of doubling of serum creatinine level, need for dialysis, or death was similar for telmisartan ($N = 1147$ [13.4%]) and ramipril ($N = 1150$ [13.5%]; hazard ratio [HR] = 1.00), but was increased with combination therapy ($N = 1233$ [14.5%]; HR = 1.09).[50] However, it is important to stress that this study did not have adequate power to address this issue.

7.5. Direct renin inhibition

Recently Aliskiren, the first oral direct renin inhibitor, has been developed for treatment of hypertension, which makes it feasible to block the RAS at the first rate-limiting step in the RAAS cascade, and without an increase in plasma renin activity. The renoprotective effect of adding a renin inhibitor to optimal renoprotective treatment with losartan 100 mg was demonstrated in the AVOID (Aliskiren in the evaluation of proteinuria in Diabetes) study in which 599 patients with type 2 diabetes received Aliskiren or placebo for 6 months showed a reduction in albuminuria of 20% compared to placebo.[51]

In a subsequent double-blinded ALTITUDE trial which assigned the patients to Aliskiren (300 mg daily) or placebo as an adjunct to an ACEI or an ARB, although Aliskiren reduced the mean urinary albumin-to-creatinine ratio and systolic and diastolic blood pressure significantly, there was an increased risk of hyperkalemia and hypotension and the trial had to be prematurely terminated after a median of 32.9 months. The study concluded that the addition of Aliskiren to the standard ACEI or ARB therapy in type 2 diabetics with high risk of cardiovascular and renal outcomes was not beneficial and may even be harmful.[52]

7.6. Mineralocorticoid blockade

Activation of the RAAS results in sodium and water retention mediated by aldosterone which exerts deleterious effects on the kidneys and vasculature by promoting inflammation, fibrosis and podocyte injury leading to albuminuria and renal dysfunction.[53] Mineralocorticoid receptor blockade (MRB) by spironolactone along with lisinopril was shown to reduce albuminuria by 34%, twice as high as compared to losartan and lisinopril combination.[54] However, spironolactone and eplerenone have been found to be associated with a high incidence of hyperkalemia, especially in patients with diabetes and/or nephropathy. Close monitoring of potassium level is, therefore, warranted.

7.7. Lipid control

Dyslipidemia in diabetics contributes to progression of CKD, particularly high triglycerides and low HDL-C appear to be associated with a deterioration in kidney function.[55] Recently concluded SHARP trial using a combination of simvastatin and ezetimibe reduced the risk of major vascular events in patients with chronic kidney disease, however, it failed to show the reduction in albuminuria and the risk of progression to ESRD.[56] A post-hoc analysis from the ASCOT trial did not show any change in proteinuria with rosuvastatin.[57] The effect of fenofibrate on macrovascular and microvascular outcome was evaluated in the FIELD study, which included 9795 type 2 diabetic patients.[57] There was no effect on progression of urinary albumin excretion alone.

7.8. Dietary protein restriction

Short-term studies in type 1 diabetic patients with normoalbuminuria, microalbuminuria, or macroalbuminuria have shown that low-protein diet (0.6–0.8 g/kg/day) reduces urinary albumin excretion and hyperfiltration independently of changes in glucose control and blood pressure.[58,59] Longer-term trials in type 1 patients with diabetic nephropathy suggest that protein restriction reduces the progression of kidney function.[60,61] Currently a dietary protein intake of 0.8 g/kg body weight per day is recommended in the Kidney Disease Outcomes Quality Initiative guidelines for patients with diabetes and chronic renal disease stages 1 through 4.[62]

7.9. Smoking

The onset and progression of diabetic kidney disease is hastened by smoking. Smoking results in accumulation of reactive oxygen species and a loss of kidney redox homeostasis culminating in a range of structural and functional changes in the kidney. The prevalence of micro- and macroalbuminuria and renal dysfunction (GFR < 60 mL/min/1.73 m^2) is high in diabetics who smoke.[63] Cessation of smoking through education and counseling, use of smoking cessation delivery systems and nicotine replacement therapy appears to be effective at preventing progression of early nephropathy in patients with type 2 diabetes.[64]

7.10. Weight loss

Increased body mass index (BMI) in diabetics has been associated with an increased incidence and rate of progression of CKD as well as an increased risk of renal cell carcinoma and nephrolithiasis.[65] Weight loss improves glycemic control and reduces proteinuria and microalbuminuria[66] as well as reduces the risk of cardiovascular disease through beneficial effects on blood pressure, dyslipidemia and serum markers of inflammation.[67] The National Kidney Foundation (NKF) recommends a target BMI of 18.5–24.9 for patients with diabetes and CKD.[36] The weight loss goal should be tailored to each patient and is achieved by various surgical and non-surgical measures comprising dietary restriction, increased physical activity, anti-obesity medications and counselling.[22] Bariatric surgery is considered in diabetics with a BMI greater than 35.[68]

7.11. New treatment options

New options are needed to treat diabetic nephropathy despite the success of the aforementioned treatment modalities. Vitamin D analogues, Sulodexide, Tranilast, Protein kinase C inhibition, Advanced glycation end product cross-link breakers, Pyridoxamine, Benfothiamine, Pentoxifylline, Thiozolidinediones, Endothelin antagonist, and Connective tissue growth factor inhibition are being tried in various clinical and preclinical trials.

8. Non-diabetic renal disease

In addition to diabetic nephropathy, wide spectrum of non-diabetic renal diseases (NDRD) is reported to occur in patients with type 2 diabetes mellitus. These include glomerular diseases other than that due to diabetes, vascular diseases, tubulointerstitial diseases and cystic diseases. The clinical findings suggesting the presence of some of these have been discussed earlier prompting timely consideration of renal biopsy and therapeutic intervention.

From an observational study in India, Prakash et al[69] showed a prevalence of NDRD in 12.3% of their type 2 diabetic patients. Both non-diabetic glomerulopathy (47%) and tubulointerstitial nephropathy (53%) occurred with nearly equal frequency in them. There was a recovery of renal function in 47% of those patients following institution of appropriate treatment. In yet another study, Soni et al[70] highlighted a similar high prevalence of NDRD in patients with type 2 diabetes. Among those 42.5% had isolated NDRD, 30% had a superimposed diabetic glomerulosclerosis and the remaining 27.5% comprised of isolated diabetic glomerulosclerosis. The indications for renal biopsy included nephrotic syndrome (34.37%), acute renal failure (30.62%), rapidly progressive renal failure (15%), absence of retinopathy (11.87%), hematuria (6.25) and acute on chronic renal failure (1.87%). Acute interstitial nephritis was diagnosed in 18.1% of the patients, 17.24% had post-infectious glomerulonephritis, membranous nephropathy and focal segmental glomerulosclerosis were seen in 11.20% and 7.75% of the patients, respectively. The mean duration of diabetes in those with isolated NDRD was significantly lower (5.37 years).

Based on our hospital-records, 39 biopsies were performed in diabetic patients during the past one year. Indications for biopsy were unexplained renal failure (*n*-17, 43.5%), nephritic syndrome ($n = 11$, 28%), rapidly progressive renal failure ($n = 8$, 20.5%) and nephrotic syndrome ($n = 3$). Out of these, isolated diabetic nephropathy was found in 11 patients (28.2%), 4 (10.2%) had associated FSGS along with diabetic nephropathy and remaining 24 (61.5%) had isolated non-diabetic renal disease. Majority of those with NDRD had acute interstitial nephritis (33.33%), FSGS was seen in 16.67% of the subjects, minimal change disease and ATN were diagnosed in 12.5% each, membranous nephropathy and hypertensive nephrosclerosis in 8.33% and Ig A nephropathy and immune complex disease occurred in 4.17% of the patients.

9. Conclusion

Diabetic nephropathy is the most common cause of ESRD. Emphasis should be laid upon to detect diabetic nephropathy during its initial stages to prevent or delay onset of complications and improve outcomes. A multipronged therapeutic approach based on optimal glycemic control, intensive antihypertensive therapy, inhibition of RAAS, statins and aspirin is pivotal in its management. Non-diabetic renal disease is seen in significant number of diabetics with kidney involvement and needs to be considered in the appropriate setting for prompt detection and intervention. Importance should be given to micro- or low-levels of albuminuria (30–299 mg/d) which is associated with endothelial dysfunction and enhanced cardiovascular morbidity and mortality.

Conflicts of interest

All authors have none to declare.

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