

In Brief

Diabetic nephropathy is the most common cause for end-stage renal disease and for patients entering into chronic dialysis care. It occurs in 25–40% of patients with diabetes. Risk factors include hyperglycemia, hypertension, genetic predisposition, glomerular hyperfiltration, proteinuria, the renal renin-angiotensin system, advanced glycation end-products, and possibly reduced nephron number and lipid disorders. Prevention of diabetic nephropathy is crucial. Tight control of diabetes, blood pressure treatment to systolic pressure of < 130 mmHg, reduction of proteinuria, and treatment with drugs that inhibit the renin-angiotensin system are all associated with prevention of or delay in progression of diabetic kidney injury.

Prevention of Progression in Diabetic Nephropathy

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A quarter of a century ago, C.E. Mogensen¹ made the unique observation that lowering blood pressure in patients with type 1 diabetes and diabetic nephropathy reduced the rate of loss in kidney function. In that study of five insulin-dependent proteinuric men with long-standing diabetes, blood pressure was lowered with combinations of furosemide, prazosin, hydralazine, and β -blockers. This observation presaged what has become a crucial intervention in diabetic nephropathy: that lowering systemic blood pressure has been repeatedly shown to alter the course of diabetic kidney disease. Great progress has been made in understanding some of the other mechanisms of this disorder and in delaying its clinical expression and preventing its progression.

The importance of diabetic nephropathy as a cause for patient morbidity and mortality is well known. Diabetic nephropathy occurs in ~ 30% of people with type 1 diabetes and 25–40% of people with type 2 diabetes, often irrespective of glycemic control. Diabetic nephropathy is the single most common cause of end-stage renal disease (ESRD) in the United States, accounting for > 50% of new cases of renal failure. Patients who have diabetes and reach ESRD have a poor prognosis because of high cardiovascular events. Thus, early identification of patients who have

diabetes and are at high risk for nephropathy is mandatory in order to prevent the development or progression of diabetic nephropathy.

This article will review what is known about the major mechanisms and risk factors promoting renal injury in diabetes and will summarize the evidence-based recommendations for preventing progression.

MECHANISMS OF RENAL INJURY IN DIABETES

The mechanisms of renal injury in diabetes are listed in Table 1 and discussed in more detail in this section.

Hyperfiltration Injury

What is known about how renal disease develops and progresses has changed in recent years. Previously, it

Table 1. Mechanisms in Diabetic Nephropathy

Hyperglycemia
Systemic hypertension
Glomerular hyperfiltration
Early, with onset of diabetes
Late, with renal injury and nephron loss
Reduced nephron number
Genetic/racial
Proteinuria
AGEs
Renal RAS
Lipid abnormalities?

was thought that kidney injury was simply the result of various insults such as immune complexes, ischemia, toxins, or, in the case of diabetes, some metabolic product (e.g., advanced glycosylation end products [AGEs]). Now, however, we know that progressive renal disease is caused by the combination of an initial or ongoing injury and a final common pathway of maladaptive response to that injury, a response that involves changes in glomerular hemodynamics and the release of cytokines and vasoactive hormones.

Research has shown that the following sequence of events leads to chronic kidney failure. Most renal diseases result from an initial injury that causes a loss of functioning nephrons. Each remaining nephron must then work harder, filtering more blood per minute to maintain homeostasis. To do this, the kidney secretes intrarenal vasoactive hormones, such as prostaglandin E₂, that preferentially dilate afferent arterioles and other hormones, such as angiotensin and catecholamines, that constrict efferent arterioles. Each glomerulus therefore receives more blood at a higher pressure and therefore filters more fluid into tubules. This situation, called hyperfiltration, damages the glomerular capillary in subtle ways, produces mesangial cell and glomerular basement membrane injury, and stimulates release of cytokines. All of these effects can produce further relentless injury and scarring of the remaining nephrons with further nephron loss. In addition, most renal diseases are accompanied by systemic hypertension and proteinuria, both of which are thought to accentuate this ongoing maladaptive intrarenal response. Systemic hypertension, in the setting of a glomerulus with dilated afferent and constricted efferent arterioles and abnormal basement membrane permeability (the hyperfiltration state), causes even greater degrees of glomerular pressure and injury. Proteinuria results in increased proximal tubular protein uptake, which causes an inflammatory response in the interstitium.

Diabetic renal disease begins not with loss of nephrons, but rather with glomerular hyperfiltration and increased glomerular filtration rate (GFR). This hyperfiltration, which has been shown to be present in early phases of both type 1 and type 2 diabetes, may exist for several years.^{2,3}

Several studies have shown that hyperfiltration is associated with the degree of hyperglycemia.

However, hyperfiltration does not always predict the future development of kidney injury in diabetes. In vulnerable patients destined for diabetic kidney disease, GFR begins to decrease as microalbuminuria appears. When overt proteinuria occurs, most individuals with diabetes have clinically decreased GFR. At this point in the course of diabetic kidney disease, loss in nephrons occurs, with the maladaptive events described above. Although the overall GFR is decreased, the glomerular filtration rate per nephron is increased, and hyperfiltration injury continues. This leads to further nephron loss, proteinuria, glomerular and interstitial scarring, and progressive renal failure.

Although diabetes is often accompanied by hyperglycemia, hypertension, and altered lipids, surprisingly, most individuals with type 1 or type 2 diabetes do not develop diabetic nephropathy. This suggests that other factors are involved.

Genetic Factors

It is clear that there are genetic factors in the risk for diabetic nephropathy. Data from the Diabetes Control and Complications Trial (DCCT)⁴ have shown that up to 35% of patients develop diabetic nephropathy, regardless of their level of glycemic control. Seaquist et al.⁵ showed that siblings of patients with type 1 diabetes who also have diabetes have a fourfold greater chance of developing diabetic nephropathy. In African Americans, Freedman et al.⁶ have also shown that ESRD is five times higher in relatives of patients with type 2 diabetes with ESRD. Among diabetic Pima Indians, 14% of descendants of parents without nephropathy develop diabetic nephropathy, whereas the incidence of nephropathy is 23% if one parent had proteinuria and 46% if both parents had nephropathy.⁷

These observations alone do not prove a genetic contribution for diabetic nephropathy but may illustrate a socioeconomic/cultural clustering. However, several investigators employing molecular genetic techniques have performed linkage analyses to explain the vulnerability for diabetic nephropathy. Thus far, evidence for linkage to diabetic nephropathy has been detected on chromosomes 3q, 10q, and 18q.⁸

Reduced Number of Nephrons

Several animal and human studies⁹⁻¹¹ have shown that reduced numbers of glomeruli at birth are associated with the eventual development of hypertension or kidney disease. The suggestion is that for individuals who start with a reduced number of nephrons, any subsequent renal injury will render them more vulnerable to progressive nephropathy. Diabetes in pregnant rats diminishes kidney weight and nephron number in their offspring.^{12,13} This finding can be imitated by exposing pregnant rats to hyperglycemia at the time fetal renal tissue is developing. If this is also true for humans, hyperglycemia in pregnant women may predispose their children to both hypertension and renal disease.

AGEs

In the setting of diabetes and longstanding hyperglycemia, free amino groups of proteins are nonenzymatically modified by glucose and its metabolites to form Schiff bases that eventually lead to the formation of AGEs. AGEs may produce functional changes in the kidney by crosslinking with the glomerular basement membrane and other vascular membranes.¹⁴ AGE-binding proteins may also be involved. The best defined of these is the receptor for AGEs (RAGE).¹⁵ Binding of AGEs to RAGEs activates cell signaling mechanisms coupled to increased transforming growth factor β (TGF- β) and vascular endothelial growth factor (VEGF) expression, which are increased in diabetic nephropathy and are thought to contribute to diabetes complications.^{16,17}

Several recent studies have shown that angiotensin receptor blockers (ARBs) and ACE inhibitors reduce AGEs and alter functioning of RAGEs.^{18,19} These effects suggest that these drugs provide renal protection by inhibiting the expression of TGF- β and VEGF mediated by AGEs and RAGEs that leads to the endothelial injury and fibrosis that is so characteristic of diabetic nephropathy.

Hyperglycemia

The hyperglycemic state itself is known to be a significant risk factor for diabetic nephropathy. Glycemic control in both type 1 and type 2 diabetes has been associated with reduced appearance of diabetic nephropathy (microalbuminuria).^{20,21} The reasons for this are likely multiple. At least

two clinical observations inform us about possible mechanisms.

The first is that the hyperglycemic state seems to sensitize the endothelium to injury from elevated blood pressure. In type 2 diabetes, lowering blood pressure, regardless of the type of agent used to do so, retards the onset and progression of diabetic nephropathy.²² In type 1 diabetes, Lurbe et al.²³ have noted that an insufficient decline in nighttime blood pressure (nondipping) preceded the onset of microalbuminuria. The second observation is that successful pancreas transplant that results in normal insulin regulation and normoglycemia is associated with a reversal of the lesions of diabetic nephropathy.²⁴

Proteinuria

Proteinuria accompanies most progressive renal diseases. Proteinuria, either microalbuminuria or macroalbuminuria, accompanies diabetic nephropathy. In general, the greater the proteinuria, the more likely the disease will progress. Many have considered proteinuria as simply a marker of significant renal injury. Recent studies,^{25,26} however, suggest that the proteinuria itself may contribute to progression of renal disease.

Any glomerular injury that increases the permeability of the glomerular basement membrane will allow plasma proteins to escape into the urine, resulting in proteinuria. Some of these proteins are ingested by proximal tubular cells, initiating an inflammatory response that contributes to interstitial scarring. Several investigators²⁶⁻²⁸ have shown that lisinopril and mycophenolate significantly reduce proteinuria-induced inflammatory injury as well as the rate of disease progression in normal rats with 1-5/6 nephrectomy (a procedure that reduces functioning kidney tissue to < 25% of normal). This information implies that any therapy, such as treatment with an ACE inhibitor or ARB, that reduces proteinuria may have a benefit beyond that brought about by reduction in blood pressure or alteration of glomerular hemodynamics.

Renal Renin-Angiotensin System

Past observations have shown that diabetes is a low-renin state, yet diabetic nephropathy seems responsive to pharmacological blockade of the renin-angiotensin system (RAS). It is now well appreciated that a local

(renal) RAS exists and is activated in diabetic individuals in the proximal tubular epithelial cells,²⁹ mesangial cells,³⁰ and the podocytes.³¹ It is this intrarenal RAS that may explain the difference in dose-response curves for blood pressure lowering and lowering of urinary protein excretion, namely, that higher doses are needed for urinary protein lowering in experimental animals and humans.³²

Systemic Hypertension

Of all of the mechanisms contributing to diabetic nephropathy, reduction of blood pressure has been clearly shown to be an important and powerful intervention. Multiple-treatment clinical trials in type 1 and type 2 diabetes have confirmed that reducing blood pressure is associated with decreased progression of diabetic nephropathy. In type 2 diabetes, blood pressure lowering independent of the antihypertensive agent used retards onset and progression of diabetic nephropathy.²² In animal models of diabetes, the degree and severity of diabetic nephropathy is strongly linked to systemic blood pressure, being more marked in the obese type 2 model than in the normotensive type 1 model (streptozotocin-induced diabetes).^{33,34} In individuals with diabetes who have disordered autoregulation of the microcirculation of the retina and kidney, systemic hypertension causes barotrauma with endothelial injury.

Lipid Abnormalities

Patients with diabetes have a variety of disorders of plasma lipids. These lipid abnormalities are known to contribute to cardiovascular risk. The role of lipids in diabetic nephropathy is not clear. In animals with reduced nephron number, dietary-induced hypercholesterolemia worsens glomerular injury.³⁵ Cholesterol-lowering drugs given to Zucker rats were associated with attenuation of glomerular lesions.³⁶ Thus far, a controlled trial to investigate whether lipid lowering will be beneficial in diabetic nephropathy has not been reported.

TREATMENTS FOR REDUCING DIABETIC NEPHROPATHY

From the above discussion, it is clear that diabetic nephropathy is the result of several contributing mechanisms, not all of which are operative in most individuals with diabetes. Clearly, prevention of diabetes is the surest

way to prevent diabetic nephropathy. At this time, prevention of type 1 diabetes is not possible. Genetic factors in type 2 diabetes, if proven, are not yet modifiable. As will be reviewed below, aggressive treatment of patients with cardiovascular risk factors can reduce de novo type 2 diabetes. If hyperglycemia during embryonic development is shown to cause reduced nephron numbers in humans, prevention of hyperglycemia during pregnancy may be protective from future renal injury, but this deduction has not been tested.

At the moment, glycemic control, blood pressure lowering, and inhibition of the RAS are the major treatment strategies once diabetes is present (Table 2). What has research shown to guide our treatments?

Preventing the Onset of Diabetes

Several large studies³⁷⁻⁴⁰ have solidly documented that both ACE inhibitors and ARBs lower the risk of de novo type 2 diabetes. These studies were criticized because in some studies ACE inhibition or ARB therapy was compared to diuretics or β -blockers, agents that could have increased the appearance of diabetes and thus made the ACE inhibition or ARB agents appear more effective.

This issue was clearly resolved by the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial.⁴¹ In this trial, the use of the ARB valsartan versus amlodipine clearly demonstrated a reduction in the appearance of type 2 diabetes. VALUE compared an ARB with amlodipine, which is not known to have any adverse effect on the development of diabetes. Possible explanations for the favorable effect of inhibition of RAS on de novo diabetes comes from a study by Lau et al.⁴² showing that RAS is present in β -cells of the pancreatic islets, that there is dose-dependent inhibition of glucose-stimulated insulin release by angiotensin 2, and that this suppression is completely reversed by pretreatment with the angiotensin type 1 receptor antagonist losartan but not by angiotensin type 2 receptor blockade.

Preventing the Appearance of Diabetic Nephropathy

Glycemic control

One of the earliest markers for diabetic nephropathy is microalbuminuria.

Table 2. Evidence-Based Interventions to Prevent Development of Diabetes or Prevent Diabetic Nephropathy

Goals	Patient Type	Intervention	Medication	Studies/Trials
Prevention of diabetes	High-risk for cardiovascular disease Nondiabetic patients	Blood pressure reduction Heart protection	Ramipril Valsartan ACE inhibitor Losartan	HOPE ⁴⁰ VALUE ⁴¹ ALLHAT ³⁷ LIFE ³⁹
Prevention of the appearance of microalbuminuria	Type 1 diabetes	Glycemic control	Insulin	DCCT ²¹
	Type 2 diabetes	Blood pressure reduction Glycemic control	No trial evidence for benefit Oral hypoglycemics	UKPDS ²⁰ Nakamura ⁴⁶ Imano ⁴⁷ Wolfenbuttal ⁴⁸
Prevention of progression of diabetic nephropathy	Type 1 diabetes	Blood pressure reduction	Trandolapril Enalapril Valsartan	BENEDICT ⁵⁴ ABCD ²² MARVAL ⁶⁰
	Type 2 diabetes		Captopril Losartan Irbesartan Ramipril ACE inhibitor	Lewis et al. ⁶¹ RENALL ⁶² IDNT ⁶³ Micro-HOPE ⁵⁶ ABCD ²²

ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; LIFE, Losartan Intervention For Endpoint reduction in hypertension study

Because the presence of microalbuminuria is thought to be a manifestation of renal and generalized endothelial injury and strongly predicts progressive diabetic nephropathy and cardiovascular risk, preventing its development is likely to be associated with prevention of progressive diabetic nephropathy and possibly of cardiovascular disease. Hence, in diabetes, the appearance or presence of microalbuminuria is used as an important indicator of effective treatment intervention.

In type 1 and type 2 diabetes, the DCCT²¹ and the U.K. Prospective Diabetes Study (UKPDS)²⁰, respectively, have shown a direct linear relationship between hyperglycemia and both the development (as evidenced by microalbuminuria) and progression of diabetic nephropathy (progression to macroalbuminuria or increasing serum creatinine) in patients who already have diabetes. Both studies showed that tight glycemic control was associated with a reduction in the appearance of microalbuminuria. In the latter trial, any decrease of hemoglobin A_{1c} (A1C) by 1% was accompanied by a 37%

decrease in the incidence rate of micro- or macroalbuminuria and retinal complications. These and many other observations have resulted in a recommendation from the American Diabetes Association (ADA) that renoprotective glycemic values are A1C < 7%, preprandial blood glucose 90–130 mg/dl, and postprandial peak < 180 mg/dl.⁴³

The oral hypoglycemic drugs rosiglitazone and pioglitazone, both thiazolidinediones (TZDs), are used in the treatment of type 2 diabetes. These drugs are agonists of the peroxisome proliferator-activated receptors (PPARs). PPARs are nuclear hormone receptors and transcription factors. Three different subtypes have been identified. These have been found to be crucial factors in regulating diverse biological processes, including lipid metabolism, insulin sensitivity, and cell growth and differentiation.⁴⁴

One of these subtypes, PPAR- γ , is also present in glomerular mesangial cells.⁴⁵ When compared to oral hypoglycemic agents, including metformin, glyburide, and glibenclamide, all antidiabetic TZDs exhibit similar

glycemic control but also seem to provide superior protection against diabetic nephropathy.^{46–48} This protection is likely a result of the systemic effect on glycemic control as well as a direct local renal effect on mesangial cell function, possibly related to the unique actions of these drugs on PPAR- γ . Support for this conclusion comes from studies in animal models of both type 1 and 2 diabetes, wherein PPAR- γ agonists have been shown to improve diabetic nephropathy.^{49–52}

In summary, it appears that angiotensin blockade reduces the onset of diabetes in high-risk populations. Tight glycemic control in diabetic patients lessens the appearance and progression of diabetic nephropathy. PPAR agonists may provide additional protection against diabetic nephropathy beyond that attributed to glycemic control.

Blood pressure control

The EUCLID (Eurodiab Controlled Trial of Lisinopril in Insulin Dependent Diabetes) study⁵³ in type 1 diabetic subjects did not detect any difference in the appearance of

microalbuminuria in patients treated with lisinopril versus placebo. However, in a study of 1,204 subjects with hypertension and nonalbuminuric type 2 diabetes, Ruggenenti et al.⁵⁴ compared trandolapril alone, trandolapril plus verapamil, verapamil alone, and placebo in preventing the appearance of microalbuminuria. Trandolapril alone and in combination with verapamil were much more effective in preventing the appearance of microalbuminuria than verapamil alone or placebo. This benefit occurred even though the levels of blood pressure control achieved were identical in all groups, suggesting that inhibition of the RAS provided protection in addition to that resulting from lowering of blood pressure. The Appropriate Blood Pressure Control in Diabetes (ABCD) trial²² found significant reduction in the development of microalbuminuria in normotensive but not hypertensive type 2 diabetic patients treated to the same goal blood pressure with either nisoldipine or enalapril.

In the UKPDS, tight blood pressure control did not reduce the development of microalbuminuria in type 2 diabetic subjects.⁵⁵ In the Microalbuminuria Cardiovascular Renal Outcomes (MICRO)-Heart Outcomes Prevention Evaluation (HOPE) substudy⁵⁶ there was no difference in the development of microalbuminuria between groups who received ramipril and placebo.

In summary, the above clinical trials do not clearly show that blood pressure control in type 1 diabetic patients lessens the appearance of microalbuminuria. In type 2 diabetes, at least two of the trials do indicate that lowering blood pressure is associated with reduction in the appearance of microalbuminuria, and they also suggest that this is best achieved with an angiotensin-inhibiting regimen that may provide protection beyond that resulting from blood pressure control alone.

Prevention of Progression in Diabetic Nephropathy

Several studies have clearly shown that in both type 1 and type 2 diabetic patients who already have microalbuminuria, ACE inhibition is effective in reducing renal progression. It has been proposed that the benefit is independent of blood pressure. Nonetheless, in most studies of type 1 diabetes, the treatment has been compared to placebo, and there have been slight

but significant differences in blood pressure.⁵⁷ In the MICRO-HOPE study⁵⁶ of type 2 diabetic patients, microalbuminuric patients who received ramipril had reduced progression rate to proteinuria. However, significant differences existed in blood pressure between groups. In the ABCD trial,⁵⁸ aggressive blood pressure control slowed progression to proteinuria in normotensive but not hypertensive patients with type 2 diabetes.

In the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study,⁵⁹ patients with microalbuminuria were protected from renal progression. Patients who received 300 mg of irbesartan daily for 24 months had a 70% risk reduction versus placebo, whereas the blood pressure achieved was basically identical. In addition, the patients who received high-dose irbesartan had a greater regression to normoalbuminuria (34%) than did the ones receiving 150 mg of irbesartan (24%) or placebo (21%). The Microalbuminuria Reduction With Valsartan (MARVAL) trial⁶⁰ compared the effects of valsartan and amlodipine in 322 patients who had type 2 diabetes and microalbuminuria. After 24 weeks, patients treated with an ARB had a greater reduction in microalbuminuria and in regression to normoalbuminuria.

It is in patients with overt diabetic nephropathy (macroalbuminuria and abnormal GFR) that blood pressure reduction, usually with an ARB or ACE inhibitor, has dramatically improved the renal prognosis.

In patients with type 1 diabetes, ACE inhibition has been shown to reduce doubling of serum creatinine (DSC) reaching ESRD, and death: 409 patients with overt nephropathy were randomized to receive either captopril or placebo for 4 years. Captopril was associated with a 48% risk of DSC, which was thought to be independent of a small but significant difference in blood pressure between the groups.⁶¹

In type 2 diabetes, two large randomized long-term trials have shown that ARBs are effective in slowing progression of diabetic nephropathy. In the Reduction of Endpoints in NIDDM With the Angiotensin Antagonist Losartan (RENAAL) study,⁶² 1,513 patients were randomized to either losartan or placebo (in addition to conventional therapy, excluding ACE inhibitors and ARBs) and followed for 3.4 years. Compared to the placebo group, patients who received losartan

had a risk reduction of 25% for DSC and 28% for reaching ESRD. In the Irbesartan Diabetic Nephropathy Trial (IDNT),⁶³ 1,715 patients were randomized to receive irbesartan, amlodipine, or placebo (in addition to conventional therapy excluding ACE inhibitors, ARBs, and calcium channel blockers) and followed for 2.6 years. Irbesartan-treated patients had a risk reduction for DSC of 33% compared to the placebo group and of 37% compared to the amlodipine group. Furthermore, both irbesartan and losartan were associated with greater reductions in albumin excretion rates than seen in other treatment groups. Overall, these studies have shown that nephroprotection with ACE inhibitors and ARBs occurs over and above what might be expected with reduction of blood pressure.

These studies have led the ADA to recommend the use of ARBs for the treatment of patients with type 2 diabetes, proteinuria, and microalbuminuria, whereas ACE inhibitors are indicated for patients with type 1 diabetes.⁴³ We are still lacking large trials of ACE inhibition in type 2 diabetic patients with proteinuria and of ARBs in type 1 diabetes. Despite this lack of trial data, the National Kidney Foundation has recommended that either ARBs or ACE inhibitors be used for patients with diabetes regardless of the presence of hypertension.⁶⁴ This recommendation is made because both classes of drugs interrupt the RAS, which is known to be an important mechanism in diabetic nephropathy. Furthermore, patient intolerance to one class of these drugs may be avoided by substituting the other class without losing the potential benefit of the RAS inhibition. Several small studies have suggested that combining ACE inhibitors and ARBs may afford even more protection or regression of diabetic nephropathy, but further large trials are needed.

SUMMARY

Following are the key therapeutic strategies for diabetic nephropathy.

1. Glycemic control to A1C < 7% reduces the appearance of diabetic kidney disease.
2. Blood pressure reduction to < 130/80 mmHg with ACE inhibitors or ARBs reduces the appearance of diabetic nephropathy in type 2 diabetes but is not proven to do so in type 1 diabetes.
3. Slowing the progression of diabetic nephropathy has been demonstrated

with blood pressure lowering (to < 130/80mmHg) with ACE inhibition in type 1 and type 2 diabetes and by ARB treatment in type 2 diabetes.

4. The protective effect of ACE inhibition or ARB therapy has been shown to be the result of both blood pressure reduction and direct drug effect.
5. In patients with diabetic nephropathy and mild to moderate azotemia, therapy with ACE inhibitors or ARBs may cause up to a 25% increase in serum creatinine within 4 weeks of initiation of therapy. Increases in serum potassium may also be seen. The rise in serum creatinine does not nullify the protective effects of ACE inhibitor or ARB therapy. Serum potassium elevations may be modified by a low-potassium diet and inclusion of diuretics in the antihypertensive regimen.

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