Diabetic nephropathy (DN) is one of the most common renal disorders seen in the El Paso County area. DN is a grave complication of diabetes mellitus (DM) and it is also the leading cause of end stage renal disease (ESRD) in the United States (US) and other developed countries. Over the past three decades, there has been an epidemic increase in obesity, metabolic syndrome and type 2 DM. Today in the US, around 75% of men and about 67% of women are either overweight or obese, this is also reflected in a significant increase in the number of patients with DN. DN is a progressive disorder caused by damage to the glomerular capillaries and has five stages. The overt clinical phase of DN is preceded by many decades of microalbuminuria. This in turn, is a predictor of future micro- and macrovascular diseases. The final stage of DN is ESRD. When a patient reaches ESRD it becomes a significant socioeconomic burden to the patients, their families, and the health care system. The morbidity and mortality due to diabetic nephropathy are almost twice as high as those of the non-diabetic with ESRD and the overall prognosis for diabetics is the worst of all ESRD patients.

This review will encompass basic information about: 1) epidemiology including local statistics; 2) the natural history and stages of diabetic nephropathy; 3) pathogenesis; 4) risk factors; 5) diagnosis; 6) clinical manifestations; 7) treatment essentials and 8) conclusions.

1. Epidemiology:
The Centers for Disease Control and Prevention (CDC) estimated that in 2012 about 29.1 million Americans or 9.3% of the populations had DM. About 8.1 million of individuals with DM were undiagnosed. Type 1 DM (T1DM), formerly known as insulin-dependent diabetes mellitus (IDDM), is due to minimal or absent pancreatic insulin secretion. It accounts for about ten percent of diabetics and it occurs most often in children and young adults. Type 2 DM (T2DM), previously known as non-insulin dependent diabetes mellitus (NIDDM), is characterized by insulin resistance. Usually occurring in overweight adults over 30, T2DM is the most common type of diabetes. More than thirteen million Americans have glucose intolerance, about one third to one half of whom remains undiagnosed. One in two people with diabetes do not know they have the disorder.

Diabetes and its associated microvascular and macrovascular complications, represent a major public health problem. DM is the seventh leading cause of death in the US. Every 7 seconds 1 person dies from DM. Direct and indirect costs exceed 245 billion dollars each year due to this disease. The prevalence of diabetic nephropathy (DN) and associated ESRD in El Paso County area is one of the highest in the nation and of the American southwest.

In 1982, DN accounted for 27% of patients with ESRD in the US and rose to 36% by 1992 and to about 44% in 2011. On December 12, 1995 there were 257,266 Medicare patients in the US with ESRD and 31.4% of them were diabetics, with a point prevalence rate of 303 per million. The incidence count during 1995 was 68,870 and 40.4% were diabetics, with an incidence rate of 104 per million. In the same year, 40.4% of Texans with ESRD, had diabetes as the primary diagnosis. In 1998 there were 19,474 Texans with ESRD and 46.9% were diabetic or a total of 9136 ESRD diabetics. In 2012 the number of prevalent cases of ESRD was 636,905 (hemodialysis 408,711, peritoneal dialysis 40,631 and transplant 186,303). The incidence of ESRD in the US in 2012 was 359 per million population and the prevalence (number of ESRD patients per million population on December 31, 2012) was 1976. The number of ESRD patients in El Paso county has also shown a dramatic increase from 585 (12/31/1995), to 769 (12/31/1997), to 769 (12/31/1997). The point prevalence in El Paso on 12/31/99 was 919. Out of the 919 cases of ESRD in El Paso 59% were diabetics or 542 (498 type 2 and 44 type 1). In 2014 the point prevalence was 2145 patients with ESRD, 63% or 1357 due to DN (1302 type 2 and 55 type 1).

2. Natural History and Stages of Diabetic Nephropathy
Mogensen and associates have described five stages of the progression of DN in T1DM (see Table 1). The evolution of DN in T2DM Type 2 is less well defined, but in general may follow a similar course. The stages may be blurred since microalbuminuria or proteinuria is often present in many Type 2 diabetic patients at the time of the initial diagnosis, including 3% of newly diagnosed type 2 DM that have macroalbuminuria.

Stage I: Hyperfiltration and Nephromegaly. The kidneys in-
strongly on the duration of diabetes. Worsening hypertension and renal insufficiency develops and are associated with glomerular sclerosis and fibrosis. The prevalence of ESRD is about 40% with T1DM versus 20-30% in T2DM. Approximately half of T2DM develop proteinuria twenty to forty years after diagnosis of diabetes but not everyone ends up in ESRD, some succumb to other microvascular and macrovascular disorders, so far, the reasons are unknown.

3. Pathogenesis:
Four main theories have been proposed to explain the pathogenesis of diabetic nephropathy. 

1. Hyperglycemia is the most important causative factor of DN. It acts directly by inducing hyperfiltration, intraglomerular hypertension and hypertrophy. Hyperglycemia also leads to alterations in tubuloglomerular feedback and abnormalities in polyl (e.g., sorbitol) metabolism. A high A1C and poor metabolic control are associated with hyperfiltering kidneys and glucose toxicity. Hyperglycemia also affects the hexosamine pathway and facilitates the formation of advanced glycosylation end-products (AGE) and might induce reactive oxygen species, monokines, chemokines, increased protein kinase C activity, changes in metalloproteinases and growth factors, which mediate tissue injury.

2. A hormonal Imbalance occurs due to lack of insulin and in some cases hyperinsulinemia plus an increase of intracellular signaling pathways, growth hormone, and glucagon. In addition, altered concentrations or responsiveness to angiotensin II, endothelin, growth factors, catecholamines, increased pro-renin, prostaglandins and nitric oxide have been found in DN. These may promote cellular and glomerular hypertrophy as well as mesangial expansion.

3. Renal Hemodynamic Changes induced by disturbances in glomerular hypertension and glomerular hyperfiltration. Hyperfiltration is mediated by greater relaxation of the afferent arterioles in the glomeruli and leads to increased glomerular blood flow and elevated glomerular capillary pressure. Hyperfiltration is the result of renal hypertension. Hypertension increases transglomerular protein filtration, inducing proteinuria and mesangial deposition of circulating proteins. As a consequence, mesangial expansion and glomerulosclerosis result in gradual destruction of surviving nephrons. A positive feedback stimulus for compensatory hyperfiltration is then initiated, which leads to a further increase in GFR and progressive renal injury.

4. Genetics. Both Type 1 and Type 2 tend to cluster in families. At present, we cannot predict which patients will develop DN. Type 1 diabetic patients with siblings who have DN carry more than a 70% risk of developing DN. Type 2 diabetic patients have a hereditary predisposition for or against development of DN.

<table>
<thead>
<tr>
<th>Stage and Features</th>
<th>Time Course</th>
<th>Structural Renal Changes</th>
<th>Glomerular Filtration Rate (GFR)</th>
<th>Urinary Albumin (mg/24hr)</th>
<th>Progression to the Next Stage</th>
<th>Blood Pressure</th>
<th>Reversible with Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Early Hypertrophy and Hyperfunction</td>
<td>Present at time of diagnosis</td>
<td>Usually None</td>
<td>20-40% Hypertension</td>
<td>&lt;30</td>
<td>100%</td>
<td>Normal</td>
<td>Yes</td>
</tr>
<tr>
<td>II Silent Stage, Early Glomerular Lesions Normal Albuminuria</td>
<td>5-10 years post diagnosis</td>
<td>Increased GMB and mesangial volume</td>
<td>20-30% Hypertension</td>
<td>&lt;30</td>
<td>35-40%</td>
<td>Normal</td>
<td>Yes</td>
</tr>
<tr>
<td>III Incipient Diabetic Nephropathy Microalbuminuria</td>
<td>Typically found after &gt; 7 years</td>
<td>Increased GBM mesangial matrix, minimal sclerosis</td>
<td>20-30% Hypertension</td>
<td>30-300</td>
<td>80-100% increased during exercise</td>
<td>Probably</td>
<td></td>
</tr>
<tr>
<td>IV Overt Diabetic Nephropathy, Macroalbuminuria</td>
<td>Detected after 20-40 years in 50% of patients</td>
<td>Often nodular glomerulosclerosis, K-W lesion</td>
<td>GFR 1 mL/min/month</td>
<td>&gt;300, later Nephrotic Range</td>
<td>75-100% Abnormal</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>V End Stage Renal Disease (ESRD) or ESKD</td>
<td>Present after 8-30 years</td>
<td>Glomerular sclerosis, schisosis</td>
<td>GFR ↓↓↓ &lt;10 mL/min/m</td>
<td>&gt; 3 g of protein but variable</td>
<td>Death occurs in &lt; 10 years</td>
<td>High</td>
<td>No</td>
</tr>
</tbody>
</table>

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However, DN is likely polygenic disease and its progression is probably related to multiple polymorphisms with variable effect sizes.

4. Risk Factors:
Multiple factors have been identified or proposed that place individuals at increased risk for developing DN and its progression. The most important factors are poor glycemic control, uncontrolled hypertension, family history of DM, race & ethnicity, and smoking. Other putative factors are shown in Table 2. However, they are not consistently present in all cases.11-15

<table>
<thead>
<tr>
<th>Elevated Blood Pressure (Hypertension)</th>
<th>Smoking</th>
<th>Long Duration of DM, Retinopathy, High Dietary Protein Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor Glycemic Control (High Level of Insulin Resistance)</td>
<td>Racal Factors, African American, Mexican American, Native American, Asian</td>
<td>Increased: Glycosylated Hemoglobin, Protein, Na+/K+ ratio, Red Cell SOD Activity, Oxidant, Proinflammatory and Metabolic parameters</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Genetic Predisposition, Smoking, Certain drugs</td>
<td>Male Gender (Europe, Australia)</td>
</tr>
<tr>
<td>Albuminuria and/or Proteinuria</td>
<td>Family History of DM &amp; Cardiovascular Events</td>
<td>Activation of Signal Transduction Molecules &amp; Cytokines: TNF-α, IL-1</td>
</tr>
</tbody>
</table>

5. Diagnosis:
Most individuals are asymptomatic throughout the early stages of diabetic nephropathy. The typical features of the five stages of DN are summarized in Table 1. The initial diagnostic tests should focus on early detection of the urinary albumin excretion rate (UAER) and the development of incipient nephropathy (Table 3). This has been simplified and replaced in the latest ADA guidelines to two categories using a spot urine collection to determine a urine albumin-to-creatinine ratio (UACR). Normal is less than 30 mg/g of creatinine and increased albumin excretion when the UACR is equal or more than 30 mg/g of creatinine.16

<table>
<thead>
<tr>
<th>Urinary Albumin Excretion Rate</th>
</tr>
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<tbody>
<tr>
<td><strong>OVERNIGHT</strong></td>
</tr>
<tr>
<td>albumin to creatinine ratio (mg/g)</td>
</tr>
<tr>
<td>Normal albuminuria</td>
</tr>
<tr>
<td>Microalbuminuria</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
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</table>

In T1DM microalbuminuria is diagnosed when the albumin excretion rate is 20-200 mcg/min or mg/L, detected in two out of three determinations over a 3-6 month interval, or an equivalent 24 hour urine excretion of 30-300 mg/day. Macroalbuminuria, or overt nephropathy, is present when UAER is more than 200 mcg/min reproduducible in two out of three separate collections over six months, or more than 300 mg/day.1

Recently, the National Kidney Foundation and the ADA have updated previous KDOQI clinical practice guidelines for diabetes and CKD.15-18 It replaces prior albuminuria categories based on the albumin creatinine ratio (ACR in mg/g) into 3 categories: A1: ≥30 mg/g, normal to mildly increased; A2: ≥30-300 mg/g, moderately increased (formerly microalbuminuria) and A3: ≥300 mg/g, severely increased (includes nephrotic syndrome ≥2000). These can be combined with the known GRAF categories labeled as G1 to G5: expressed in ml/min/1.73 m². In brief G1: >90, normal or high; G2: 60-89, mildly decreased; G3a: 45-59, mildly to moderately decreased; G3b: 30-44, moderately to severely decreased; G4, 15-29, severely decreased; G5 ≤15 or treated by dialysis, kidney failure. For example a patient can be classified as G3ba3. This corresponds to a GFR of 45 to 59 that has also severely increased albuminuria UACR of more than 300 mg/g of creatinine.

Several studies have shown that the onset and course of DN can be significantly delayed by early intervention. Therefore, it is recommended that the albuminuria level should be checked at diagnosis and annually in patients with T2DM. In patients with T1DM microalbuminuria should be checked at puberty and annually after 5 years duration of diabetes.1 Confirmation tests are recommended since false positive tests may occur with urinary tract infections, hypertension, massive obesity, excessive physical exercise, stress, severe hyperglycemia, congestive heart failure, fever, etc. At the office setting, microalbuminuria can be easily checked with two commercially available immunochemical dipsticks: Roche’s Micral or Miles’ Bumins-Test. The Micral Test immunoassay employs a strip that is immersed in the urine sample for 5 seconds, producing a color reaction after 1 to 5 minutes. This result is compared with color blocks on the vial label corresponding to the albumin concentration found in mg/L. If the microalbuminuria is present, a 24-hour urine collection should be done to check for protein and creatinine clearance. If more than 300 mg of albumin is found, or if the serum creatinine is ≥1.8 mg/dl, a nephrological evaluation is suggested to exclude other causes of proteinuria. If no other causes are present and if microalbuminuria persists, the patient should be treated for DN with intensified glycemic control, risk reduction and normalization of blood pressure if applicable. But once microalbuminuria is documented, irrespective of blood pressure, treatment with an ACE inhibitor is recommended or an ARB if the patient has side effects.1,10-16

Overt diabetic nephropathy is characterized by proteinuria, hypertension, edema and renal insufficiency. About 50% of type 1 diabetic patients develop significant nephropathy. However, in type 2 it occurs only in around 5-20%, depending mostly on ethnic factors. Renal histopathological changes may include minimal or no glomerular changes, glomerular mesangial expansion, nodular glomerulosclerosis (the classic lesions of the Kimmelstiel-Wilson disease), or nonspecific vascular changes, and tubulointerstitial disease.1 The earliest evidence of nephropathy is microalbuminuria.8 This later progresses to clinical proteinuria or macroalbuminuria, overt or gross proteinuria (dipstick positive ≥300 mg/day or more than 200 mg/min), which is often accompanied by hypertension and progression to a nephrotic range proteinuria (≥3.5 g/day). Eventually macroalbuminuria leads to decreasing GFR, about 1 ml/min per month, with an inexorable rising of the serum creatinine until ESRD appears.

Several renal function tests can be used to follow the progression of DN. The creatinine clearance (Ccr) is a widely used direct methods of estimating GFR. It is based on results of a carefully timed urine collection, a period usually of 24 hours. Invalid studies may result from an incomplete collection or failure to achieve bladder emptying at the start and end of the collection period. Serum creatinine (Scre) and blood urea nitrogen (BUN) tests are indirect measures of GFR. However, they are less sensitive markers of renal function.
function than the creatinine clearance. In early DN the reported normal range may not show an increase until approximately half of the renal function is lost and overt nephropathy is established. There are other nuclear medicine studies, such as 125I-iodoalbumin, 51Cr-EDTA, 99mTc-DTPA that can be used to estimate the GFR, but these are not widely available and are expensive. In a patient with a non-fluctuating renal function a rough assessment of the creatinine clearance can be obtained, from plasma without urination measurements, with the Cockcroft-Gault formula.19

\[
\text{Cr Clearance or } C_r (\text{mL/min}) = \frac{[140-\text{age}] \times \text{[body weight (kg)]}}{72 \times S_c (\text{mg/dL})}
\]

If the patient is a woman, the same formula is used and the result is multiplied by 0.85 to adjust for smaller muscle mass. The formulas overestimate Cr in obese patients and those on a low protein diet. For the past 10-15 years the MDRD formula that uses serum creatinine or its modifications has been used to estimate the GFR and CKD staging. Other formulas proposed use cystatin or combination with creatinine and for many investigators the CKD EPI (Chronic Kidney Disease Epidemiology Collaboration) equation is preferred. This was just reviewed by Levey et al.18 Other experts argue that CKD should be adjusted according to age and that there is an artificial increase in patients being reported as having CKD.20 Adding to this confusion, the KDOQI group experts have reviewed the staging of CKD and the prior concepts of microalbuminuria and macroalbuminuria have been replaced with moderately increased albuminuria and severely increased albuminuria respectively.17,18 I prefer the prior conceptual staging outlined in Table 1.

When the patient has advanced renal insufficiency, approaching ESRD, a closer estimate of the GFR may be done with a simultaneous 24-hour urine collection to check for creatinine and urea clearances. Usually in ESRD the creatinine clearance overestimates whereas the urea clearance underestimates the actual GFR. Thus, the arithmetic mean of the two clearance values gives an approximate estimate of the actual GFR. When this value is approaching 15 mL/min patient education, extensive counseling and preparation for renal replacement therapy should be done without delay.1,17,21

6. Clinical Manifestations:
As renal function deteriorates a pattern of signs and symptoms may become evident. Symptoms can take 5 to 10 years to appear after the kidney damage begins. Usually the symptoms are apparent when the GFR is thirty-five percent or less and when patients become nephrotic. As the kidney conditions worsen, the uremic syndrome gradually becomes apparent due to the progressive accumulation of metabolic waste products. Late symptoms at this stage include tiredness, malaise, nausea, vomiting, anorexia, pruritis and peripheral edema.1,21

Gastrointestinal signs and symptoms may include anorexia, hiccup, nausea, vomiting, gastrointestinal bleeding, gastroenteritis, and even uremic breath. Fluid and electrolyte abnormalities include weight gain, edema, metabolic acidosis, calcium, phosphorus and electrolyte imbalances. Neuromuscular abnormalities range in severity from retinopathy, muscular irritability, polyneuropathy, and fatigue to subtle changes in concentration and level of consciousness including stupor, seizures, coma. Cardiovascular and pulmonary manifestations may include hypertension, pericarditis, arrhythmias, congestive heart failure and pulmonary edema. Hematologic and immunologic abnormalities encompass fatigue, anemia, leukopenia, and increased risk of bleeding and infection. Endocrine and metabolic abnormalities may include renal osteodystrophy, carbohydrate intolerance, infertility and malnutrition. When the GFR falls below 20 mL/min the patient with DN gradually becomes catabolic and is at a greater risk of developing concomitant illnesses. Finally, when creatinine clearance falls to 10 mL/min, the patient with DN is often too ill to perform any work or maintain any livelihood without renal replacement therapies.1,11,18,21

7. Treatment Essentials:
There are approaches directed to each different stage of the diabetic nephropathy including non pharmacologic and pharmacologic therapy.1,16,21-26

The nonpharmacologic therapy includes patient education, risk reduction, identification and management of comorbid conditions, lifestyle modifications including diet and exercise. When a patient reaches stage V diabetic nephropathy, ESRD or ESKD, the options for renal replacement therapy include hemodialysis, peritoneal dialysis and/or transplantation. In the elderly, conservative non dialytic care may be advisable, since studies have shown no real survival or medical advantages of dialytic therapies. In the 1970’s in the US and United Kingdom patients over 65 were not started on dialysis.

In the US several types of oral agents and insulins have been approved for the pharmacological treatment of diabetes mellitus. The oral agents include sulphonylureas(chlorpropamide, glipizide, glyburide/glubencalamide and glimepiride), biguanides (metformin), α-glucosidase inhibitors (acarbose, miglitol), meglitinides (repaglinide and natiglinide), the bile acid sequestrants (Colesvelam) the thiazolidinediones (pioglitazone, resiglitazone), dipeptidyl peptidase DPPI inhibitors (sitagliptin, saxagliptin, linagliptin, alogliptin), the Amylin mimetic (Pramlintides) the sodium glucose linked transporter-2 (SGLT2) inhibitors (canagliflozin, empagliflozin, dapagliflozin) and glucagon-like peptide-1 (GLP-1) inhibitors (exenatide, liraglutide, abigliptide, dulaglutide) and the Insulins: rapid acting analogs (Lispro, Aspart, Glulisine) short acting (Human Regular), Intermediate acting (Human NPH) Basal insulin analogs (Glargine, Detemir), Premixed Insulin (several types) and Inhaled Insulin (Afrezza) that have been reviewed recently.21-26 Many of these agents are not indicated in patients with CKD 3-5 due to adverse side effects.

As for preventative measures, there are three that can be taken to slow the development of DN. The primary prevention aims to forestall or delay the progression from normoalbuminuria to microalbuminuria. The arrest or postponement of the progression from microalbuminuria to macroalbuminuria is the aim of secondary prevention. Tertiary prevention hinders or defers the

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progression of overt DN or macroalbuminuria to ESRD and cuts
morbidity and mortality by delaying the time lag from macroalbuminuria to dialysis or transplant.

The main strategies used to prevent the progression of DN include: a) intensive glycemic control; b) effective albuminuria management; c) aggressive blood pressure control; d) smoking cessation; e) protein restriction; f) cholesterol reduction and g) reversal of endothelial dysfunction.1,13,15-16,23,26

a) Intensive glycemic control: There is now compelling evidence from the medical literature that long-term glucose control is essential. We should strive to maintain the glycosylated hemoglobin level below 7 percent. T2DM is a progressive disorder and all treatment shows secondary failure over time. Insulin therapy is often recommended when oral agents or combinations are no longer successful or not indicated. In most patients, the failure of two or three oral agents used together calls for the use of insulin alone or in addition to oral agents and these will not be reviewed here.1,14,26

Of major importance are the results of the Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications Research Group (EDIC study), which have shown the benefits of intensive therapy in delaying the onset of diabetic complications.22-28 Moreover, the United Kingdom Prospective Diabetic Study, or UKPDS,29 shows a variety of results including a twenty-six percent reduction of microvascular complications, a twenty-one percent lowering of retinopathy progression, a thirty-four percent decrease in microalbuminuria, a sixteen percent decline of myocardial infarction, and a ten percent diminution of diabetes related death, as compared with conventional therapy. Thus, intensive pharmacotherapy is effective in reducing microvascular complications. For every percentage point decrease in hemoglobin A1C there is a thirty-five percent reduction in the risk of complications, and more importantly, any reduction in hemoglobin A1C is beneficial.1,15,18,22,29

Table 4

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ADA Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average prandial glucose (mg/dl)</td>
<td>80-120</td>
</tr>
<tr>
<td>Average bedtime glucose (mg/dl)</td>
<td>100-140</td>
</tr>
<tr>
<td>HbA1C (%)</td>
<td>&lt;7</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>130/85</td>
</tr>
</tbody>
</table>

Glucose control is probably a key determinant for ESRD risk. The ADVANCE trial which is the largest clinical trial which includes follow up of 8494 patients showed that intense glucose control leads to long-term reductions in the risk of developing ESRD.10

The latest guidelines of the American Diabetes Association has endorsed optimization of glucose and blood pressure control to reduce the risks or slow the progression of DN.16 The following parameters and goals (Table 4) for patients with diabetes mellitus, previously suggested.1,11

A simplified alternative is the Pazmiño’s Rule of 100’s that include the above parameters and is based on evidence gathered from recent trials, ADA recommendations National Kidney Foundation, clinical experience and current guidelines. This rule is applied to the mean glycemic control, mean arterial blood pressure, mean LDL cholesterol and mean microalbuminuria and can be extended to other parameters (triglycerides, ideal body weight, salt intake, exercise, etc.).32

b) Effective albuminuria control is of paramount importance. Again, microalbuminuria is now called: “moderately increased albuminuria, for simplicity I abbreviated it to “mial” using the initials of the new nomenclature. At this stage, intensive diabetic control is critical. Type 1 diabetic patients with microalbuminuria or mial have a 15-20 fold predisposition to develop macroalbuminuria (now called severely increased albuminuria or I abbreviated to “sial”) after 10 years, whereas in type 2 the risk is only a 5-10 fold increase. Microalbuminuria (or mial) is a marker of endothelial dysfunction and is also a strong predictor of myocardial infarction and stroke. Thus a routine urinalysis is recommended in type 2 diabetic patients at the time of diagnosis. If the urinalysis is positive for protein, a 24 hour collection for protein and creatinine clearance is advisable for follow up and treatment. If the urinalysis is negative for protein a test for microalbuminuria or mial is needed and depending of the results an algorithm can be followed (Figure 1) as previously suggested by the American Diabetes Association.1,13

Figure 1, reprinted with permission from the ADA1,13

If the test for microalbuminuria or mial is positive, it needs to be validated one more time and thereafter treatment with any an-

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Angiotensin-converting enzyme (ACE) inhibitors is initiated. The microalbuminuria or mial test should be repeated in 4-6 weeks. If on one hand, no microalbuminuria or mial is detectable the ACE inhibitor is continued. If on the other hand, microalbuminuria or mial is still present, the dose of the ACE inhibitors should be increased. This is followed up by another determination of microalbuminuria or mial in 4-6 weeks and the dose of the ACE inhibitor should be increased (unless contraindicated) until the microalbuminuria or mial disappears or is stable in three consecutive urines.1,35

c) Aggressive blood pressure control for a patient with DN is crucial. Hypertension is the most important factor that accelerates the progression of DN. The blood pressure should be lowered gradually, after significant carotid stenotic lesions have been excluded, especially in the elderly to avoid potential complications.1 The antihypertensive and dyslipidemia therapy are very important in patients with T2DM but are beyond the scope of this discussion and have been reviewed recently. Of major importance are the findings of a 50% reduction of major cardiovascular events in type 2 diabetic patients whose target diastolic pressure was 80 mm Hg than among patients whose diastolic blood pressure was 90 mm Hg.35 Thus, it is recommended that the blood pressure in patients with DN and proteinuria of less than one gram should be 130/85 mm Hg. However, if the patient with DN has more than one gram of protein per 24 hours, the recommended blood pressure should be 125/75 mm Hg and these goals have been recently modified.1,6,21,26,35

Microalbuminuria or mial should signal the need for antihypertensive therapy. ACE inhibitors (ACEI) should be the first line of therapy for DN. If side effects appear or if the blood pressure control is not adequate, angiotensin receptor blockers (ARBs) may be used instead of, or in some cases, in addition to ACE inhibitors.1,6,21,22,25,29,35 Independent of the systemic blood pressure changes ACE inhibitors have a beneficial effect on proteinuria, GFR, vasculature, heart and kidneys. However, because of the small risk of hyperkalemia and unrecognized renal artery stenosis (<5%), serum creatinine and potassium should be monitored at the start of the treatment and one week thereafter.1 The long acting calcium channel blockers are commonly prescribed and are generally well tolerated. They are generally used in combination with other agents, but they are less effective than ACE inhibitors in reducing albuminuria and with respect to cardiac endpoints. Thereby, they should not be used as monotherapy but in combination with ACE inhibitors. Diuretics and beta blockers are also commonly prescribed, and they may have undesirable side effects and are inferior in reducing proteinuria.1,6,21,33-35

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The choice of agents in hypertensive diabetic patients is mostly based on two factors: a) the prevention of adverse cardiovascular events and b) effects of slowing or reversing the progression from one stage DN to the next. For example in the ALLHAT trial there was a lower onset of heart failure with chlorthalidone compared to amlodipine and lisinopril.36 In the ACCOMPLISH trial, an ACEI combined with amlodipine provided better protection against cardiovascular outcomes than the combination of an ACEI and low dose hydrochlorothiazide.37,38

As noted above, ACEI or ARB are the preferred initial therapy in patients with micro- or macroalbuminuria, or even in hypertensive patients without albuminuria or proteinuria. At present there are more than a dozen ACEI and more than half a dozen ARB. The reader is suggested to get thoroughly familiar with one or two agents in each group.

In general, as DN progresses, combination therapy is usually required in most patients. Carvedilol (Coreg) is a preferred beta blocker compared with metoprolol because of potential benefits on glycemic control and lower rate of progression of DN. If the patient has renal disease or heart failure a loop diuretic should be added. The goal blood pressure should be less than 140/90 mm Hg in most diabetics and ideally 130/80 mm Hg in DN patients with proteinuria more than 500 mg/day. Occasionally a systolic pressure of less than 120 mm Hg may be considered to decrease stroke risks, but the absolute benefits attained is in 89 patients at five years and is counterbalanced by more adverse side effects, extra visits and increased cost, as noted in the ACCORD BP trial.39

To sum up, ACEIs/ARBs should be used as a first-line therapy in T1DM and T2DM if hypertension and albuminuria or mial or proteinuria or sial are present. Currently, there is no major evidence to support ACEIs/ARBs for the primary prevention of microalbuminuria and the target BP should be less than 130/80 especially in those with proteinuria. A simple guideline for the primary care practitioners is the Rule of 100’s but for the interested reader the yearly updated guidelines from the American Diabetes Association are suggested.1,15,16

In regards to the possible use of ACEI/ARB combination to maximally block the RAS, it can be done but needs to be monitored closely for adverse side effects. The CALM study looked at candesartan and lisinopril endpoints in terms of BP control and proteinuria and showed a benefit, but there was no improvement in mortality and disease outcomes.40 The NEPHRON D study found the combination of ACEIs and ARBs was associated with increased risk of adverse side effects in patients with DN41 and the On Target study showed that the combination group had worse renal function and adverse outcomes compared with the group that receive a single agent.42

As far as the use of ACEIs/ARBs for renoprotection in the context of major surgery, the decision-making should be done individually. If the indication is hypertension or myocardic heart disease it is preferable to continue them, but for renal benefit, short term discontinuation seems reasonable.

Another issue that frequently arises is hyperkalemia in patients taking ACEIs, ARB’s or combination of agents. In this situation a reduction of the doses should be tried, potassium (K) restriction should be started and loop diuretics can be used, as well as avoidance of K sparing diuretics. Kayexalate can be used temporarily. However, if the K level does not return to baseline in 2-4 weeks a discontinuation of ACEIs/ARBs should be made. In the future Patriomer, a non absorbable polymer that binds K in exchange for Ca may be a helpful adjunctive therapy.43

d) Smoking cessation should be strongly encouraged as diabetics are at increased risk of premature death from cardiovascular disorders and there is also evidence to suggest that smoking can hasten the progression of DN.44,45

e) Protein restriction remains subject to controversy as shown by the Modification of Diet in Renal Disease study group, or MDRD.44 However, there does appear to be a benefit of a modest reduction in dietary protein. Based on current data, it is advisable to recommend a protein restriction of about 1g/kg/day in patients with clinical nephropathy, approximately 10% of daily calories, with a further restriction to 0.8 g/kg/day once GFR begins to fall.5,29,35,46

f) Cholesterol reduction. Patients with DN are at high risk of cardiovascular disease and premature death. They should be screened for cardiovascular risk factors and treated accordingly. The American College of Cardiology and the American Heart Association Task force recently updated guidelines. For patients with DM and LDL cholesterol 70-189 mg/dl, the 10-year risk of atherosclerotic cardiovascular disease should be calculated. If the risk is <7.5%, moderate intensity statin therapy is suggested. If the risk is >7.5%, high intensity statin therapy is required. The latter include those with an acute coronary syndrome, prior myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attacks or peripheral arterial disease. A risk calculator is available at http://my.americanheart.org/cvriskcalculator.47

g) Reversal of endothelial dysfunction. Under normal conditions the glomerular endothelium actively regulates vascular tone, permeability to molecules and macrophages, the composition of the endothelial matrix and the proliferation of smooth muscle cells. The renin angiotensin system (RAS) plays also an important role in the regulation of vascular fibrinolysis, growth factors and matrix accumulation. The RAS interacts with the fibrinolytic system at the level of the endothelium. The endothelium is a critically important regulator of blood flow. Angiotensin Converting Enzyme (ACE) is a crucial mediator of this interaction. About 90% of ACE is tissue bound (blood vessels, heart, kidneys, CNS), and 10% is in the circulation. ACE is present on the surface of endothelial cells. Therefore ACE regulates the expression of the fibrinolytic proteins t-PA (tissue plasminogen activator) and PAI-1 (plasminogen activator inhibitor type I). Angiotensin II (A II) regulates endothelial PAI-1 production and secretion while bradykinin promotes vasodilatation by enhancing the production of t-PA. PAI-1 is particularly increased in the vasculature of patients with diabetes. Endothelial dysfunction is undoubtedly a factor in the development of the micro- and macrovascular complications seen in T1DM and T2DM.1,33-35,46

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ACE Inhibitors protect the vessel wall and produce a decrease in A II level and accumulation of bradykinin. This in turn promotes the release of nitric oxide (NO) which results in vasodilatation and relaxation of vascular smooth muscle. ACEI blunt the production of superoxide anion, decreases vascular smooth muscle cell growth and migration and platelet aggregation. They also help to maintain the fibrinolytic balance by decreasing PAI-1 and increasing t-PA levels. Thus, they may contribute to the effect of these agents in preventing ischemic cardiovascular events in patients type 2 diabetes. It is also known now that Angiotensin II is involved in matrix accumulation and induction of glomerular cell growth. Therefore, the reversal of endothelial dysfunction with ACEI, statins, and the thiazolidinediones helps to slow down the progression of DN and is an area of active investigation.1,16,33-35,46

8. Conclusions:
When a patient reaches ESRD, the appropriate steps must be taken for dialysis and/or transplantation for the patient’s survival. The patient should be referred to a nephrologist on a timely basis. In general, the nephrologist will provide patient education about choices available and initiate and supervise renal replacement therapy. The choices of renal replacement therapy are tailored to the patient’s desires and abilities.

It is imperative to avoid a late referral of the patient with DN and renal failure. Some of these patients may present as uremic emergencies, which are often associated with high morbidity and mortality. Late referrals should be avoided since they provoke a major setback to the patient with DN, who frequently has difficulty accepting the options available for ESRD. These late referrals also have a worse prognosis and they may have to rely on a temporary or inadequate vascular access and associated complications. Many of these DN patients are affected since they may lose their jobs due to the prolonged absence from work.13,33-35

In the US Medicare provides major support to the ESRD patient’s care since the enactment of a special law in 1972. Nonetheless, the purpose of the management of the patient with DN should be to provide patient’s education, intensive and appropriate medical therapy. We should aim to maintain near euglycemia and normoalbuminuria, achieve risk reduction and ideally stop or reverse the progression of diabetic nephropathy. Our ultimate goal should be to decrease the prevalence of diabetic complications in the twenty-first century.1

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Reprint Requests: Patricio Pazmiño PhD MD FACP, NIH Ctr, 1701 N. Mesa, El Paso, TX 79902-3503

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Patricio Pazmiño PhD MD FACP FASN is a Nephrologist in private practice and is the Medical Director of the Nephrology, Internal Medicine & Hypertension (NIH) Center, 1701 N. Mesa, El Paso, Texas 79902-3503.