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Diabetic Kidney Disease

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Diabetic Kidney Disease: Introduction & Burden of Disease

Diabetic Kidney Disease (DKD) formerly known as diabetic nephropathy is the most common cause of end-stage renal disease (ESRD) and death in patient with diabetes (Fox, 2012; Himmelfarb, & Tuttle, 2013).

More than 100,00 people are diagnosed with chronic kidney disease in the United Sates annually. More than 20 million (or 1 in 10 Americans) are currently living with some level of chronic kidney disease (National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK], 2016).

44% of newly diagnosed cases of chronic kidney disease are caused by diabetes (NIDDK, 2016).

DKD in the US population has risen from 2.2% to 3.3% from1998 to 2008 (Fox, 2012), while those receiving treatment for ESRD has increased 18 fold from 1980 to 2008 (Toth-Manikowski, & Atta, 2015)

The annual cost of DKD in the United states in 2009 was estimated at $18 billion (Reutens, 2013). This cost rose to over $40 billion by 2009 (NIDDK, 2016).

At risk populations include African Americans, American Indians, and Hispanics/Latinos, all of whom develop diabetes and chronic kidney disease at higher rates than Caucasians. As of now, the scientific community is able to say why these groups are more at risk. However, it is thought to be an interplay of heredity, diet, and comorbid conditions. High blood pressure and hyperglycemia increase the risk of developing DKD (NIDDK, 2016).

Underlying Pathophysiology

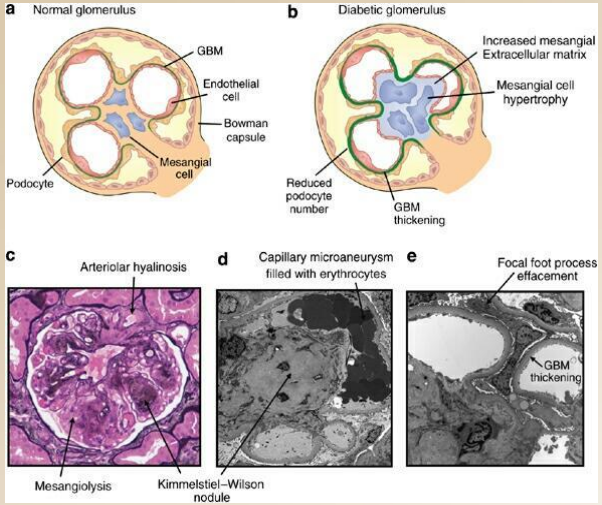

Figure 1: Glomerular changes related to underlying pathophysiology. Retrieved from: http://www.kidney-international.org/cms/attachment/2043439544/2056050861/gr3.jpg

Various pathophysiologic pathways lead to:

- Renal tissue mesangial cell changes
- Extracellular matrix production
- Cellular oxidative stress
- Cellular destruction
- Increase vascular permeability
- Hyperfiltration
- Albuminuria.
- All of which causes:

Glomerular Dysfunction: Decrease GRF

Table 1. KDOQI (2002)*clinical practice guidelines for chronic kidney disease with clinical presentation. ** no change with update in 2015; http://www2.kidney.org/professionals/kdoqi/guidelines_ckd/p9-approach/html*

Table 139. Stages of Chronic Kidney Disease: Clinical Presentations

Stage	Description	GFR Range (mL/min/1.73 m²)	Clinical Presentations*
	At increased risk	≥60 (without markers of damage)	CKD risk factors
1	Kidney damage with normal or ↑ GFR	≥90	Markers of damage (Nephrotic syndrome, Nephritic syndrome, Tubular syndromes, Urinary tract symptoms, Asymptomatic urinalysis abnormalities, Asymptomatic radiologic abnormalities, Hypertension due to kidney disease)
2	Kidney damage with mild ↓ GFR	60–89	Mild complications
3	Moderate ↓ GFR	30–59	Moderate complications
4	Severe ↓ GFR	15–29	Severe complications
5	Kidney Failure	<15 (or dialysis)	Uremia, Cardiovascular disease

* Includes presentations from preceding stages. Chronic kidney disease is defined as either kidney damage or GFR <60 mL/min/1.73 m² for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies

Pathophysiologic Processes

Genetic Factors: ESRD-associated single nucleotide polymorphism (SNP) found by GENIE study: an intronic SNPAF4/FMR2 family member 3; and an intergenic SNP on chromosome 15q26 (rs12437854) (Reidy, et al., 2014). Sharma, et al (2013) found that kidney tissue from DKD patients had less mitochondrial DNA, and lower gene expression of PGC1-a, a regulator of mitochondrial biogenesis. The researchers also found 12 urine metabolite that support suppression of mitochondrial metabolism.

Histologic Changes: At the cellular level, expansion in the mesangial cells form a thickened basement membrane. In turn, there is hyperfiltration and glomerulosclerosis with Kimmelsteil-Wilson nodules. Hypertrophic changes in podocytes allow for increased filtration of albumin (Reidy, Kang, Hostetter, & Susztak, 2014; Toth- Manikowski, & Atta, 2015). These changes have been attributed to diabetic angiopathy, aging, atherosclerosis, hypertension, and episodes of acute kidney injury (Toth-Mankowski, & Atta, 2015).

Hemodynamic Changes: Hemodynamically, there is an elevation of Angiotensin II and Endothein-1 (ET-1) which results in changes in mesangial cells and extracellular matrix production that increase vascular permeability and hyperfiltration, increasing inflammation, and hypertension (Toth- Manikowski, & Atta, 2015).

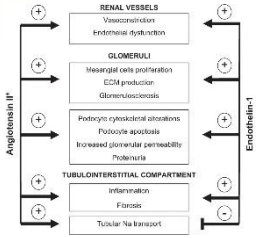

Figure 2: Effects of Angiotensin II and Endothelin I http://ajpregu.physiology.org/content/310/10/R877.figures-only

Metabolic Changes: Four metabolic pathways were noted by Toth-Mankowski and Atta (2015) that are upregulated due to increasing glycolysis of hyperglycemia. These pathway (the polyol pathway, the hexamine pathway, advances glycation end products, and PKC pathway) result in damage to the renal system in some manner.

Polyol Pathway is upregulated due to hyperglycemia. Glucose is normally converted to sorbitol via the NADPH-dependent enzyme aldose reductase, and is then converted to fructose. When upregulated, the polyol pathway the reduction of glucose to sorbitol at a higher rate results in decreased intercellular NADPH. In turn the antioxidant glutathione is decreased, contributing to increased intracellular oxidative stress which may end in cellular apoptosis.

Hexosamine pathway stems from the third step of glycolysis that results in production of glucosamine-6-phosphate, which is used as a substrate to increase transcription of inflammatory cytokines: tumor necrosis factors-a (TNF-a) (see AGEs below) and transforming growth factor-b1 (TGF-b1). TGF-b1 promote renal cell hypertrophy and increased mesangial matrix components.

Production of advanced glycation end products (AGEs) result from irreversible glycation of proteins that are present with intercellular hyperglycemia. AGEs damage cells by modifying protein function that leads to increased permeability of glomerular basement membrane, expansion of the renal extracellular matrix , and increasing pro-inflammatory cytokines (IL-1, IL-6, TMF-a).

Activation pf protein kinase C (PKC) stems from the 4th step of glycolysis. PKC increases activity of prostaglandin E2, and NO leading to vasodilation, contributing to glomerular hyperfiltration.

Signs and Symptoms

The diagnosis of kidney disease is made by measuring albumin levels in the urine (albuminuria). However, this is detected long before the patient shows any overt signs of kidney disease. Albuminuria is classified by the amount in urine in a 24 hour period. Microalbuminuria is 30-300 mg of albumin, while macroalbuminuria is greater than 300 mg (National Kidney Foundation, 2009).

Glomerular filtration rate (GFR) is also calculated in order to monitor the function of the kidney (see Table 1).

Other signs and symptoms that the patient may notice earlier in the disease process are weight gain and ankle swelling. Later signs and symptoms are described below (National Kidney foundation, 2015).

Significance of Pathophysiology

Understanding the complex interconnection of the pathophysiology of DKD will allow the advance nurse practitioner to appropriately treat the patient at risk for DKD.

The pathophysiology includes cellular changes brought on by genetic factors, dysfunction in the glycolysis pathways, renal mesangial changes, extracellular matric production, oxidative stress and destruction, increased vascular permeability and hyperfiltration. These mechanisms generate the resulting albuminuria and decreasing GFR that are hallmark for DKD..

Nursing Implications

Investigating the pathophysiology underlying DKD has allowed advanced nurse practitioners to adequately screen patient with diabetes for albuminuria prior to overt clinical symptomology.

Glycemic control is paramount to the treatment of the diabetic patient in order to stall the progression of kidney disease.

The National Kidney Foundation (2015) recommends annual screening for patients with diabetes to include Hgb A1C, blood pressure, BUN, creatinine, and urine albumin levels. Treatment for high blood pressure with ACE inhibitors or ARBs to interrupt the renin-angiotensin-aldosterone system (RAAS) is also recommended.

Pt education regarding the need for glycemic and blood pressure control is also needed. Advanced practitioners must address diet as a means of not only glycemic control, but also as a major influence on blood pressure levels, and obesity.

Conclusion

It is well documented that DKD not only creates a large financial burden on the United States, but greatly adds to the morbidity and mortality of the patient with diabetes. DKD is a complex interplay of various pathophysiologic mechanisms. The advanced nurse practitioner must fully understand the mechanism at play in DKD and the resulting insult to the renal tissue. This understanding allows the advanced nurse practitioner to properly educate and treat patients at risk for DKD.

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