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Diabetic Nephropathy

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Introduction

Diabetes mellitus (DM) is a group of metabolic diseases characterized by an increase in blood glucose levels, or hyperglycemia, resulting from inadequate secretion or action of insulin preventing glucose from being absorbed into the cells (McCance and Huether, 2014).

- Nearly 9.3% of the U.S. population and 26% of Americans age 65 and older had diabetes
- Diabetes is the 7th leading cause of death in the U.S (Centers for Disease Control and Prevention, 2014).
- One of the major complications of DM includes diabetic nephropathy, also known as diabetic kidney disease

Diabetic Nephropathy is defined as progressive disease or damage to the kidneys caused by the metabolic and hemodynamic changes in diabetes. This condition is characterized by persistent albuminuria, a decline in the glomerular filtration rate (GFR), and elevated arterial blood pressure (Jaipaul, 2013).

- Leading cause of end-stage renal disease, and associated with increased cardiovascular mortality (Jaipaul, 2013).
- Approximately 30% of individuals with type 1 diabetes mellitus and 40% of individuals with type 2 diabetes mellitus will develop diabetic nephropathy (McCance and Huether, 2014).

As a healthcare professional, having an understanding of the complex pathophysiology of diabetic nephropathy and the most appropriate screening, prevention, and treatment options available is vital for the management of the diabetic patient population. Development of this progressive kidney disease would have life-long effects on quality of life as meticulous monitoring and treatment is required to slow the progression of the disease.

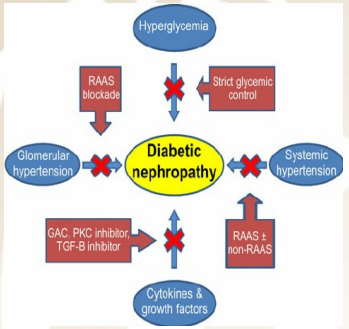


Image retrieved from https://www.researchgate.net/figure/51725608_fig1_Figure-1-Pathogenesis-of-diabetic-nephropathy-and-steps-to-slow-its-onset-and

Pathophysiology

The main pathophysiology changes in diabetic nephropathy comprises of a complex network of events leading to damage of the glomerular filtration membrane (GFM), irreversible damage to glomerular capillaries and loss of kidney function (Sego, 2007). The GFM is comprised of three layers: the glomerular endothelium, the glomerular basement membrane, and the epithelial podocytes, that permits a highly selective ultrafiltration of the blood plasma and maintains a balance of vasoconstriction and dilation. Other key changes include: mesangial cell expansion, Kimmelstiel–Wilson nodules, glomerulosclerosis, and tubular interstitial fibrosis (Zheng and Zheng, 2015). These changes occur due to both genetic and environmental factors associated with diabetes, the most significant being hyperglycemia and hypertension. An early physiologic abnormality is glomerular hyperfiltration and intra-glomerular hypertension, accompanied by the onset of microalbuminuria (Mora-Fernández, 2014). The cellular elements of the kidney respond to hyperglycemia by various pathways: hemodynamic, metabolic, and inflammatory (Toth-Manikowski and Atta, 2015).

Hemodynamic Pathway:

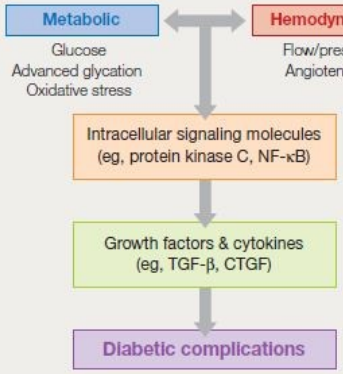
The hemodynamic dysfunction includes intra-glomerular hypertension and hyperfiltration as a result of efferent arteriole vasoconstriction due to activation of the renin-angiotensin-aldosterone-system (RAAS) (Toth-Manikowski and Atta, 2015). Hyperglycemia stimulates the RAAS resulting in increased intra-glomerular capillary pressure. Angiotensin II actives pathways which induce inflammation, renal cell growth (mesangial expansion) and apoptosis of podocytes (Mora-Fernández, 2014). Hyperglycemia also impairs the autoregulatory mechanism that maintains normal glomerular perfusion and glomerular filtration rate (GFR), initially resulting in an increase in GFR. This elevated intra-glomerular pressure stimulates several responses within the glomerular capillary bed: thickening of endothelial mesangial cells and the glomerular basement membrane, and loss of selective permeability. Microalbuminuria develops as well as impairment of nitric oxide (NO) transport (Sego, 2007).

Metabolic Pathway:

In metabolic dysfunction, hyperglycemia leads to increased glycolysis, the process by which cells break down glucose to make energy, which upregulates four pathways. The polyol pathway results in the conversion of glucose to sorbitol, causing decreases in nitric oxide and contributing to intracellular stress and apoptosis. Sorbitol is then converted into fructose which has been identified as a nephrotoxin leading to increased proteinuria, decreased GFR, and increased superoxide levels and inflammatory cytokines (Toth-Manikowski and Atta, 2015). The second hexosamine pathway stems from a step in glycolysis in which fructose-6-phosphate is converted to glucosamine-6-phosphate and used to increase inflammatory cytokines: tumor necrosis factor-a and transforming growth factor-B1 which promotes renal cell hypertrophy (Toth-Manikowski and Atta, 2015). The third pathway includes the formation of advanced glycation end-products (AGEs), which is a bond between glucose and proteins. AGEs directly accelerate the vascular complications of diabetes. Intracellular AGEs lead to expression of cytokines and growth factors that contribute to glomerular sclerosis and tubulointersitial fibrosis. Extracellular AGE accumulation can cause structural changes including a thickening of the glomerular basement membrane (GBM) due to leukocyte and platelet adhesions and accelerate endothelial dysfunction resulting in leakage of serum proteins (Mora-Fernández, 2014). AGEs also have the ability to bind to pro-inflammatory receptors; modulating cell functions, activating the production of cytokines, and increases generation of reactive oxygen species (ROS) (Toth-Manikowski and Atta, 2015). The final pathway stems from the final step in glycolysis in which glyceraldehyde-3-phosphate is converted into a cofactor that activates protein kinase C (PKC). PKC increases activity of prostaglandin E2 and nitric oxide (NO) causing vasodilation of the afferent arteriole leading to glomerular hyperfiltration (Toth-Manikowski and Atta, 2015). PKC also contributes to GBM thickening and extracellular matrix (ECM) accumulation which alters the capillary permeability allowing larger protein molecules (albumin) to enter the vasculature (Mora-Fernández, 2014).

Inflammatory Pathway:

The inflammatory pathway is caused by the chronic inflammatory state of diabetics (Hojs, Ekart, Bevc, Hojs, 2015). Damage to renal cells release signals that triggers remodeling processes activating immune cells of the innate and adaptive response systems. Inflammatory cytokines increase vascular endothelial cell permeability, influence GMB thickening, and fibrosis develops and progresses (García-García et al, 2014).



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Significance of Pathophysiology

Understanding the pathophysiology of chronic diabetic nephropathy will allow health care providers to identify risk factors and provide appropriate preventative treatments such as medication regimens, laboratory testing and screenings; as well as aid in early detection, diagnosis, and maintenance to slow further progression of the disease.

Signs and Symptoms

- Asymptomatic in early stages
- Sustained microalbuminuria followed by macroalbuminuria
- Hypertension
- Dependent Edema
- Nausea, vomiting, weakness
- Increased BUN and/or creatinine

Table 1. Clinical stages of diabetic nephropathy[3]

Stage	GFR	UAE	Blood pressure	Years
1. Hyperfiltration	Super normal	<30 mg/day	Normal	0 - 5
2. Microalbuminuria	High normal - normal	30 - 300 mg/day	Rising	5 - 15
3. Overt proteinuria	Normal - decreasing	>300 mg/day	Elevated	10 - 20
4. Progressive nephropathy	Decreasing	Increasing	Elevated	15 - 25
5. ESKD	<15 mL/min	Massive	Elevated	20 - 30

ESKD = end-stage renal disease; GFR = glomerular filtration rate; UAE = urinary albumin excretion.

Image retrieved from http://www.scielo.org.za/scielo.php?script=sci_arttext&pid=S0256-95742015000300034

Implications for Nursing

- Provide diabetes education and support, including education related to complications such as diabetic nephropathy
- Patients must have an understanding of medications, diet, laboratory values, and basic knowledge of anatomy and physiology associated with their disease to facilitate better understanding and compliance
- Diabetic nephropathy is very common, asymptomatic until late, and should be considered in all patients with diabetes: screening should begin immediately after diagnosis in patients with type 2 diabetes and within 5 years of diagnosis for type 1 diabetics (Lewis and Maxwell, 2014)
- Measure albumin in a spot urine sample, collected either as the first urine in the morning or at random (Gross et al., 2015)
- Monitor renal function: GFR and serum creatinine (Gross et al., 2015)
- Obtain renal ultra sound looking for hypertrophy (Butt, Hall, and Nurko, 2010)
- When prevention fails and the diabetic state does exist, rigid control of hyperglycemia (maintain HbA_{1c}at ≤ 7.0) with a combination of with diet, exercise, and medications
- Treat BP aggressively, usually beginning with angiotensin inhibition (Sego, 2007)
- Other considerations include: lipid management, protein restriction, vitamin D supplementation (Quiroga, Arroyo, & de Arriba, 2015)
- In patients with kidney failure, emotional support and education regarding renal replacement therapy is important, as well as continued strict glycemic control to prevent further complications including: diabetic retinopathy, peripheral vascular disease, cardiovascular disease, etc (Sego, 2007).

Conclusion

The most common cause of ESRD in the United States today is diabetic nephropathy, and the incidence of type 2 diabetes is increasing. Several factors contribute to renal damage, including hyperglycemia, hypertension, and a genetic predisposition in some patients. The best treatment for diabetic nephropathy is prevention. Once nephropathy is present, progression cannot be avoided, only delayed. The earliest clinical indicator of renal damage is microalbuminuria; therefore, any patient diagnosed with diabetes should be screened for diabetic nephropathy at regular intervals with sensitive tests (Evans and Capell, 2015). Patient education, strict glucose and blood pressure control including medications and lifestyle changes, and regular testing is essential for adequate treatment of the diabetic patient to prevent this incurable complication.

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