Complications of Diabetes Mellitus

Presented by: John Avolio, Clinical Pharmacist
Certified Geriatric Pharmacist

Overview

- Diabetes can cause acute complications, such as severely elevated hyperglycemic, diabetic ketoacidosis, hyperosmolar coma, and hypoglycemia (dizziness, confusion, weakness, tremors) which can lead to seizures, coma, and even irreversible brain death.

- However, over time, the progressive long-term complications of diabetes can bring devastating and life-threatening consequences to patients.

- Appropriate screenings and treatment of these complications must take place in a timely manner to prevent worsening of the complications.

Mechanisms of Chronic Complications

- Complications of diabetes mellitus are far less common and less severe in people who have well-controlled blood sugar levels.

- Chronic elevation of blood glucose levels leads to damage of blood vessels (angiopathy).

- The endothelial cells lining the blood vessels take in more glucose than normal, since they do not depend on insulin.

- Forming more surface glycoproteins than normal they cause the basement membrane of the vessels to grow thicker and weaker.
Mechanisms of Chronic Complications (continued)

- Long-term complications of diabetes that affect small blood vessels are called microvascular complications
  - Microvascular complications include, but are not limited to
    - Retinopathy
    - Nephropathy
    - Neuropathy

Microvascular Complications

- Diabetic Retinopathy Epidemiology
  - Most common microvascular complication, contributing to over 10,000 cases of blindness per year
  - Almost all patients with type 1 diabetes and approximately 60% of those with type 2 diabetes will develop some degree of retinopathy within 20 years of diagnosis
  - The prevalence of retinopathy at clinical diagnosis of diabetes is approximately 21% in the United States
  - Clinically significant retinopathy can be detected as early as 7 years before the diagnosis

Diabetic Retinopathy Signs & Symptoms

- Diabetic Retinopathy often has no early warning signs
- Even macular edema, which may cause vision loss more rapidly, may not have any warning signs for some time
- In general, a person with macula edema is likely to have blurred vision, making it hard to do things like read or drive
- In some cases, the vision will get better or worse during the day
Diabetic Retinopathy Signs & Symptoms (continued)

- The first stage, also called non-proliferative diabetic retinopathy (NPDR) there are no symptoms
  - Not visible to the naked eye
  - Patients have 20/20 vision
  - Narrowing or blocked retinal blood vessels can occur (this is called retinal ischemia, or lack of blood flow)
  - Macular edema may occur in which blood vessels leak contents into the macular region of the eye
    - Macular edema symptoms are blurring, darkening or distorted images with not the same between both eyes
    - 10% of diabetic patients will have vision loss related to macular edema

Diabetic Retinopathy Signs & Symptoms (continued)

- In the second stage, abnormal new blood vessels form at the back of the eye as a part of proliferative diabetic retinopathy (PDR)
  - Can burst and bleed and blur vision because the new blood vessels are weak
    - May not be severe the first episode, leaving just a few specks of blood or spots floating in a person's visual field though the spots often dissipate after a few hours
    - These spots are often followed within a few days or weeks by a much greater leakage of blood, which blurs vision
    - In extreme cases, a person will only be able to tell light from dark in that eye
    - It may take the blood anywhere from a few days to months or even years to clear from the inside of the eye, and in some cases will not clear
  - These types of large hemorrhages tend to occur more than once, often during sleep

Pathogenesis of Diabetic Retinopathy

- Diabetic retinopathy is the result of microvascular retinal changes

- Small blood vessels - such as those in the eye – are especially vulnerable to poor blood sugar (blood glucose) control

- An over accumulation of glucose and/or fructose damages the tiny blood vessels in the retina

- Progression of the disease may start as nonproliferative diabetic retinopathy (NPDR) and move to proliferative diabetic retinopathy (PDR)
Risk factors of Diabetic Retinopathy

- All persons with diabetes mellitus (Type 1 and Type 2) are at risk
- The longer a person has diabetes, the higher the risk of developing ocular problems
- Between 40 to 45 percent of Americans diagnosed with diabetes have some stage of retinopathy

Diagnosis of Diabetic Retinopathy

- The eye care professional will look at the retina for early signs of the disease such as:
  - Leaking blood vessels
  - Retinal swelling deposits on the retina
  - Pale, fatty deposits on the retina (exudates)
    - Signs of leaking blood vessels
    - Damaged nerve tissue (neuropathy)
    - Any changes in blood vessels

Management of Diabetic Retinopathy

- Three major treatments which are very effective in reducing vision loss
- Even people with advanced retinopathy have a 90% chance of retaining their vision when they receive treatment before the retina is severely damaged

- Treatments
  - Laser surgery
  - Injection of corticosteroids
  - Vitrectomy (removing cloudy vitreas and replacing it with saline solution)
Management of Diabetic Retinopathy (continued)

- Although these treatments are quite successful in slowing or stopping further vision loss, they do not cure diabetic retinopathy
- Caution should be exercised in treatment with laser surgery since it causes a loss of retinal tissue
- It is often more prudent to inject a corticosteroid such as triamcinolone
  - In some patients it results in a marked increase of vision, especially if there is an edema of the macula

Management of Diabetic Retinopathy (continued)

- Avoiding tobacco use and correction of associated hypertension are important therapeutic measures in managing diabetic retinopathy
- The best way of addressing diabetic retinopathy is vigilant monitoring in an effort to achieve euglycemia (normal blood glucose)

Diabetic Nephropathy Epidemiology

- A progressive kidney disease caused by angiopathy of capillaries in the kidney glomeruli
- It is due to long standing diabetes mellitus
- Is a prime indication for dialysis in many developed countries
- Diabetic Nephropathy is the most common cause of chronic kidney failure and end-stage kidney disease in the United States
Diabetic Nephropathy Epidemiology (continued)

- People with both type 1 and type 2 diabetes are at risk
- The risk is higher if blood-glucose levels are poorly controlled
- Also, people with high cholesterol have a much greater risk than others

Diabetic Nephropathy Signs and Symptoms

- Kidney failure provoked by glomerulosclerosis leads to fluid filtration deficits and other disorders of kidney function
- There is an increase in blood pressure and fluid retention in the body
- Other complications may be arteriosclerosis of the renal artery and proteinuria
- In the early stages, diabetic nephropathy has no symptoms

Diabetic Nephropathy Signs and Symptoms (continued)

- Symptoms develop in the late stages and may be a result of excretion of high amounts of protein in the urine or due to renal failure
  - Edema: swelling, usually around the eyes in the mornings; later, general body swelling may result, such as swelling of the legs
  - Foamy appearance or excessive frothing of the urine (caused by proteinuria)
  - Unintentional weight gain (from fluid accumulation)
  - Anorexia (poor appetite)
  - Nausea and vomiting
  - Malaise (general ill feeling)
  - Fatigue
  - Headache
  - Frequent hiccups
### Pathophysiology of Diabetic Nephropathy

- **Glomerular Hyperfiltration** is the basic pathophysiology in Diabetic Nephropathy
  - Leads to intraglomerular hypertension—reason that ACE inhibitors are recommended (they help prevent diabetic nephropathy by preventing this step in the disease process)
  - The earliest detectable change in the course of diabetic nephropathy is glomerular basement membrane thickening caused by glomerular hyperfiltration, followed by nodular sclerosis

### Pathophysiology of Diabetic Nephropathy (continued)

- At this stage, the kidney may leak more serum albumin (plasma protein) than normal in the urine (albuminuria)
  - This stage is called “microalbuminuria”
- As nephropathy progresses, increasing numbers of glomeruli are destroyed by progressive nodular glomerulosclerosis
  - At this stage, a kidney biopsy generally clearly shows diabetic nephropathy

### Diabetic Nephropathy Diagnosis

- The first laboratory abnormally is a positive microalbuminuria test
- Most often, the diagnosis is suspected when a routine urinalysis of a person with diabetes shows too much protein in the urine (proteinuria)
- The urinalysis may also show glucose in the urine, especially if blood glucose is poorly controlled
- Serum creatinine and BUN (blood urea nitrogen) may increase as kidney damage progresses
Diabetic Nephropathy Diagnosis (continued)

- Diagnosis is based on the measurement of urinary albumin
  - Normoalbuminuria: urinary albumin excretion <30mg / 24 hours
  - Microalbuminuria: urinary albumin excretion of 30-299mg / 24 hours
  - Clinical (overt) albuminuria: urinary albumin excretion ≥ 300mg / 24 hours

- Another diagnostic tool is glomerular filtration rate (eGFR)
  - Based on creatinine values and patients age
  - Normal eGFR is above 90ml/min/1.73m²

Diabetic Nephropathy Diagnosis (continued)

- Stages of renal damage can be identified by eGFR intervals
  - Stage 1: ≥ 90 ml/min/1.73m²
  - Stage 2: 60 – 89 ml/min/1.73m²
  - Stage 3: 30 – 59 ml/min/1.73m²
  - Stage 4: 15 – 29 ml/min/1.73m²
  - Stage 5: < 15 ml/min/1.73m²

- Diabetic nephropathy is usually preceded by the onset of diabetic retinopathy

- Evidence of nephropathy without retinopathy creates the suspicion that the renal impairment is not caused by diabetes alone

Diabetic Nephropathy Diagnosis (continued)

- Development of Diabetic Nephropathy

<table>
<thead>
<tr>
<th>Stage</th>
<th>Designation</th>
<th>Characteristics</th>
<th>Structural Changes</th>
<th>Glomerular/Renal Function</th>
<th>Blood Pressure (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Hyperfunction</td>
<td>Hyperfiltration</td>
<td>Glomerular hypertrophy</td>
<td>&lt;100</td>
<td>Normal</td>
</tr>
<tr>
<td>II</td>
<td>Normoalbuminuria</td>
<td>Normal albumin loss</td>
<td>Basement membrane thickening</td>
<td>≤10</td>
<td>Normal</td>
</tr>
<tr>
<td>III</td>
<td>Incipient diabetic nephropathy (microalbuminuria)</td>
<td>Increased albumin loss</td>
<td>Altered albuminuria correlates with structural damage and hypertrophy of remaining glomeruli</td>
<td>100</td>
<td>Increased</td>
</tr>
<tr>
<td>IV</td>
<td>Overt diabetic nephropathy</td>
<td>Clinical proteinuria</td>
<td>Advanced structural damage</td>
<td>&lt;100</td>
<td>Hypertension</td>
</tr>
<tr>
<td>V</td>
<td>Uremia</td>
<td>Kidney failure</td>
<td>Glomerular closure</td>
<td>0-10</td>
<td>High</td>
</tr>
</tbody>
</table>
## Diabetic Nephropathy Treatment

- The goals of treatment are to slow the progression of kidney damage.
- The primary treatment, once proteinuria is established, is the use of ACE inhibitor drugs, which usually reduces proteinuria levels and slows the progression of diabetic nephropathy.
- The renal protection effect is related to the antihypertensive effects in the normal and hypertensive patients, renal vasodilation resulting in increased blood flow and dilatation of the efferent arterioles.

## Diabetic Nephropathy Treatment (continued)

- Many studies have shown that related drugs, angiotensin receptor blockers (ARBs) have a similar benefit.
- Blood-glucose levels should be closely monitored and controlled:
  - May slow the progression of the disorder, especially in the very early (microalbuminuria) stages.
  - Medication to manage diabetes include oral hypoglycemic agents and insulin injections.
- Diet may be modified to help control blood-sugar levels.

## Diabetic Nephropathy Treatment (continued)

- Modification of protein intake can affect hemodynamic and nonhemodynamic injury.
- High blood pressure should be aggressively treated with antihypertensive medication.
  - This reduces the risks of kidney, eye and blood vessel damage.
- Very important to control lipid levels, maintain a healthy weight, and engage in regular physical activity.
Diabetic Nephropathy Treatment (continued)

- Patients with diabetic nephropathy should avoid taking the following drugs
  - Contrast agents containing iodine
  - Commonly used non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen, or COX-2 inhibitors like celecoxib, because they may injure the weakened kidney

- Urinary tract and other infections are common and can be treated with appropriate antibiotics

Diabetic Nephropathy Treatment (continued)

- Dialysis may be necessary once end-stage renal disease develops
  - Kidney transplantation may be considered at this stage
  - Another option for type 1 diabetes patients is a combined kidney-pancreas transplant

Diabetic Neuropathy Epidemiology

- Neuropathy results from diabetic microvascular injury involving small blood vessels that supply nerves in addition to macrovascular conditions that can culminate in diabetic neuropathy

- Globally, diabetic neuropathy affects approximately 131 million people as of 2010 (1.9 percent of the population)

- Diabetes is the leading known cause of neuropathy in developed countries, and neuropathy is the most common complication and greatest source of morbidity and mortality in diabetic patients
Diabetic Neuropathy Epidemiology (continued)

- Prevalence of neuropathy in diabetes is approximately 20%
- Diabetic neuropathy is implicated in 50 – 75% of nontraumatic amputations
- The main risk factor for diabetic neuropathy is hyperglycemia
- The progression if neuropathy is dependent on the degree of glycemic control in both Type 1 and Type 2 diabetes
- Duration of diabetes, age, cigarette smoking, hypertension, height and hyperlipidemia are also risk factors for diabetic neuropathy

Diabetic Neuropathy Signs and Symptoms

- Diabetic neuropathy affects all peripheral nerves including pain fibers, motor neurons, and the autonomic nervous system
  - It therefore can affect all organs and systems, as all are innervated

Diabetic Neuropathy Signs and Symptoms (continued)

- Symptoms vary depending on the nerve or nerves affected and may include, but not limited to the following symptoms: numbness and tingling of extremities, dysesthesia (abnormal sensation to a body part), diarrhea, erectile dysfunction, urinary incontinence, facial/mouth/eyelid drooping, vision changes, dizziness, muscle weakness, difficulty swallowing, speech impairment, fasciculation (muscle contractions), burning or electric pain
**Pathogenesis of Diabetic Neuropathy**

- Microvascular disease
  - Vascular and neural diseases are closely related and intertwined
  - Blood vessels depend on normal nerve function, and nerves depend on adequate blood flow
  - The first pathological change in the microvasculature is vasoconstriction

**Pathogenesis of Diabetic Neuropathy (continued)**

- As the disease progresses, neuronal dysfunction correlates closely with the development of vascular abnormalities, such as capillary basement membrane thickening and endothelial hyperplasia, which contribute to diminished oxygen tension and hypoxia
  - Neuronal ischemia is a well-established characteristic of diabetic neuropathy
  - Vasodilator agents (e.g., ACE inhibitors) can lead to substantial improvements in neuronal blood flow, with corresponding improvements in nerve conduction velocities

**Diabetic Neuropathy Classifications**

- Two major classifications
  - Focal and multifocal neuropathies (ex: mononeuropathy and nerve pain involving multiple lesions)
  - Symmetrical neuropathies are also known as diabetic peripheral neuropathy (DPN) [most common presentation]
Diabetic neuropathy: Effects on nerve types

- Different nerves are affected in different ways
- Sensorimotor polyneuropathy
  - Longer nerve fibers are affected to a greater degree than shorter ones, because nerve conduction velocity is slowed in proportion to a nerve’s length
  - In this syndrome, decreased sensation and loss of reflexes occur first in the toes on each foot, then extend upward
  - Usually described as glove-stocking distribution of numbness, sensory loss, dysesthesia and night time pain

Diabetic neuropathy: Effects on nerve types

- The pain can feel like burning, pricking sensation, achy or dull
- Pin and needles sensation is common
- Loss of proprioception, the sense of where a limb is in space, is affected early
  - These patients cannot feel when they are stepping on a foreign body, like a splinter, or when they are developing a callous from an ill-fitting shoe
  - Consequently, they are at risk of developing ulcers and infections on the feet and legs, which can lead to amputation
  - These patients can get multiple fractions of the knee, ankle, or foot

Diabetic neuropathy: Effects on nerve types (continued)

- Loss of motor function results in dorsiflexion, contractures of the toes, loss of muscle function that leads to contraction of the digits, called hammer toes
- These contractures occur not only in the foot but also in the hand where the loss of the musculature makes the hand gaunt and skeletal
- The loss of muscular function is progressive
Diabetic neuropathy: Effects on nerve types (continued)

- Autonomic neuropathy
  - The autonomic nervous system is composed of nerves innervating the heart, lungs, blood vessels, bone, adipose tissue, sweat glands, gastrointestinal system and genitourinary system
  - Autonomic neuropathy can affect any of these organ systems
  - The most commonly recognized autonomic dysfunction in diabetics is orthostatic hypotension, or fainting when standing up
  - In the case of diabetic autonomic neuropathy, it is due to the failure of the heart and arteries to appropriately adjust heart rate and vascular tone to keep blood continually and fully flowing to the brain

- This symptom is usually accompanied by a loss of respiratory sinus arrhythmia; the usual change in heart rate seen with normal breathing
  - These two findings suggest autonomic neuropathy
  - GI tract manifestations include gastroparesis, nausea, bloating, and diarrhea
  - Because many diabetics take oral medication for their diabetes, absorption of these drugs is greatly affected by the delayed gastric emptying
    - This can lead to hypoglycemia when an oral diabetic agent is taken before a meal and does not get absorbed until hours, or sometimes days later, when there is normal or low blood sugar already

- Sluggish movements of the small intestine can cause bacterial overgrowth, made worse by the presence of hyperglycemia
  - Leads to bloating, gas, and diarrhea
  - Urinary symptoms include urinary frequency, urgency, incontinence, and retention
  - Because of the retention of urine, urinary tract infections are frequent
  - Urinary retention can also lead to bladder diverticula, stones, reflux nephropathy
Diabetic neuropathy: Effects on nerve types (continued)

- **Cranial Neuropathy**
  - When cranial nerves are affected, neuropathies of the oculomotor nerve (cranial nerve #3) are most common
  - The oculomotor nerve controls all of the muscles that move the eye with the exception of the lateral rectus and superior oblique muscles
  - The oculomotor nerve also serves to constrict the pupil and open the eyelid
  - The onset of a diabetic third nerve palsy is usually abrupt, beginning with frontal or periorbital pain and then diplopia

- **All of the oculomotor muscles innervated by the third nerve may be affected, but those that control pupil size are generally affected the least (because of their anatomical position they are less susceptible to ischemic damage – they are closer to the vascular supply)**

- **Mononeuropathies of the thoracic or lumbar spinal nerves can occur and lead to painful syndromes that mimic myocardial infarction, cholecystitis, or appendicitis**

Diabetic Neuropathy Treatment

- Despite advances in the understanding of the metabolic causes of neuropathy, treatments aimed at interrupting these pathological processes have been limited

- With exception of tight glucose control, treatments are for reducing pain and other symptoms

- Options for pain control include tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs), anticonvulsant drugs (AEDs), classic analgesics, and physical therapy
Diabetic Neuropathy Treatment (continued)

- A systematic review concluded that tricyclic antidepressants and traditional anticonvulsants are better for short term pain relief than newer generation anticonvulsants

- A combination of these medications (ex: gabapentin plus nortriptyline) may also be superior to a single agent

- The only three drugs approved by the FDA for diabetic peripheral neuropathy are the antidepressant duloxetine, the anticonvulsant pregabalin, and the long-acting opioid tapentadol ER

Diabetic Neuropathy Treatment (continued)

- Before trying a systemic medication, some pain experts recommend treating localized diabetic peripheral neuropathy with lidocaine patches

- Tricyclic antidepressants
  - TCAs include imipramine (Tofranil), amitriptyline (Elavil), desipramine (Norpramin), and nortriptyline (Pamelor)
  - TCAs are effective at decreasing painful symptoms but render multiple side effects that are dosage dependent
  - One notable side effect is cardiac toxicity, which can lead to fatal arrhythmias

Diabetic Neuropathy Treatment (continued)

- At low dosages used for neuropathy, toxicity is rare, but if symptoms warrant higher doses, complications become more common

- Amitriptyline is most commonly used but desipramine and nortriptyline have fewer side effects

- Serotonin-norepinephrine reuptake inhibitors
  - The SSNRI duloxetine (Cymbalta) is approved for diabetic neuropathy, however venlafaxine (Effexor) is also commonly used
**Diabetic Neuropathy Treatment (continued)**

- **Anticonvulsant drugs**
  - AEDs, especially gabapentin (Neurontin) and pregabalin (Lyrica), are emerging as first line treatment for painful neuropathy
  - Gabapentin compares favorably with amitriptyline in terms of efficacy, but in clearly safer
  - The primary side effect of Gabapentin is sedation, which does not diminish over time and may, in fact, worsen
  - Gabapentin needs to be taken three times daily, and it may cause weight gain, which can worsen glycemic control in diabetics

- **Carbamazepine (Tegretol)** is effective but not necessarily safe for diabetic neuropathy

- **Topiramate** has not been studied in diabetic neuropathy, but has the benefit of weight loss, and is anecdotally beneficial

- **Classic analgesics**
  - The aforementioned drug categories are known as adjuvants and are often combined with opioids and/or NSAIDs, usually having effects greater than the sum of their parts

- **Physical Therapy**
  - Can be an effective and alternative treatment option for patients with diabetes
  - May help reduce dependency on pain relieving drug therapies
  - Certain physiotherapy techniques can help alleviate symptoms such as deep pain in the feet and legs, tingling or burning sensation in extremities, muscle cramps, muscle weakness, sexual dysfunction, and diabetic foot
  - Gait training, posture training, and teaching these patients the basic principles of off-loading can help prevent and/or stabilize foot complications such as foot ulcers