Team Medicine

10.

Diabetic complications

Writer: SadeemAldawas
Reviser1:AbdulazizAlhamad
Reviser 2: MosaedAldekhayel

Leader: Sama Al Ohali

■ Slides ■ Doctors notes ■ Additional
■ Questions ■ Summary

431 Teams

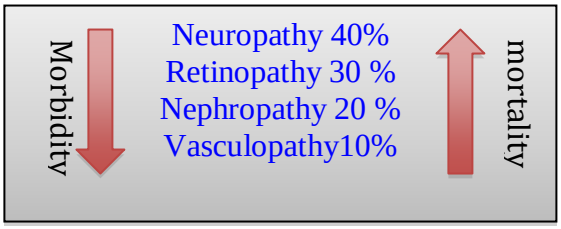
The doctor did not have slides for this lecture but he said the reference is Davidson's book so our work based on it.

LONG-TERM COMPLICATIONS OF DIABETES

The long-term results of treatment of diabetes are disappointing in many patients. Although a few diabetic patients die from acute metabolic complications (ketoacidosis and hypoglycemia), the major problem is the excess mortality and serious morbidity suffered as a result of the long-term complications of diabetes.
Excessmortality in diabetes is caused mainly by large blood vessel disease, particularly myocardial infarction and stroke. Macrovascular disease also causes substantial morbidity from myocardial infarction, stroke, angina, cardiac failure and intermittent claudication. The pathological changes associated with atherosclerosis in diabetic patients are similar to those seen in the non-diabetic population but they occur earlier in life and are more extensive and severe. Diabetes amplifies the effects of the other major cardiovascular risk factors: smoking, hypertension and dyslipidemia. Moreover, patients with type2 diabetes are more likely to have additional cardiovascular risk factors.

Causes of death in diabetes (approximate proportion)

- Cardiovascular disease 70%
- Renal failure 10%
- Cancer 10%
- Infections 6%
- Diabetic ketoacidosis 1%
- Other 3%



Pathophysiology

The histopathological hallmark of diabetic microangiopathy is thickening of the capillary basement membrane, with associated increased vascular permeability throughout the body. The development of the characteristic clinical syndromes of diabetic retinopathy, nephropathy, neuropathy and accelerated atherosclerosis is thought to result from the local response to the generalized vascular injury

Preventing diabetes complications

❖ **Glycemic control in type 1 diabetes**

In patients with type-1 diabetes, strict **glycemic control** (mean HbA1c 7%) reduced the development of retinopathy and other microvascular complications by 76% compared with conventional therapy (mean HbA1c 9%). On longer-term follow-up strict glycemic control also reduced cardiovascular events, including myocardial infarction, stroke and death from cardiovascular disease.

❖ **Glycemic control in type 2 diabetes**

In patients with type 2 diabetes, intensive glycemic control (mean HbA1c 7%) with **oral anti-diabetic drugs or insulin** reduced the development of microvascular complications, particularly retinopathy, by 25% compared with conventional treatment (mean HbA1c 8%). On longer-term follow-up there was a significant reduction in myocardial infarction and all-cause mortality.

The risk:benefit ratio of good control in certain patients.

Thus less intensive treatment may be indicated in:

- Those with impaired awareness of hypoglycemia.
- Those with severe macrovascular disease (particularly if they have a past history of myocardial infarction or cerebrovascular accident)
- Those at the extremes of life (very young children and the frail elderly)

Control of other risk factors

Randomized controlled trials have shown that aggressive management of blood pressure minimizes the microvascular and macrovascular complications of diabetes. ACE inhibitors are valuable in improving outcome in heartdisease and in preventing diabetic nephropathy .The management of dyslipidemia with a statin limits macrovascular disease in people with diabetes. This often results in the necessary use of multiple medications, which augments the problem of adherence to therapy by patients

Macrovascular complications(from step-up)

The main problem is accelerated atherosclerosis, which puts patients at increased risk of stroke, MI, and CHF. The accelerated atherosclerosis in diabetics is the reason the target BP is lower in diabetics (130/80) than in general population (140/90), and the reason the target LDL is lower in diabetics is less than 100 mg/ dL. The cause of accelerated atherosclerosis is not known, although glycation of lipoproteins and increased platelet adhesiveness/aggregation are thought to be twopotential causes. In addition, the process of fibrinolysis may be impaired in diabetic patients.

The most active cell in our body is myocardium cell which completely dependent on the insulin to get glucose and to produce energy

The manifestations of atherosclerosis include the following:

a. Coronary artery disease (CAD)
- Risk of CAD is two to four times greater in diabetic than in non-diabetic persons.
- **Most common cause of death in diabetic patients**
- Silent myocardial infarctions are common.

b. Peripheral vascular disease—in up to 60% of diabetic patients>gangrenous diabetic foot
c. Cerebrovascular disease (strokes)

* The risk of coronary events is greatly reduced if the patient can eliminate or reduce other major cardiovascular risk factors (smoking, HTN, hyperlipidemia, obesity).

Diabetic retinopathy

Diabetic retinopathy is one of the commonest causes of blindness in adults between 30 and 65 years of age in developed countries. Retinal photocoagulation is an effective treatment, particularly if it is given at a relatively early stage when the patient is usually symptomless. Expert annual examination of the fundi is therefore mandatory in all diabetic patients.

Pathogenesis

Hyperglycemiaincreases retinal blood flow and metabolism and has direct effects on retinal endothelial cells and pericyte loss,which impairs vascular auto-regulation. The resulting uncontrolled blood flow initially dilates capillaries but also increases production of vasoactive substances and endothelial cell proliferation, resulting in capillary closure. This causes chronic retinal hypoxia and stimulates production of growth factors, including vascular endothelial growth factor (VEGF), which plays a major role in stimulating the deleterious changes of endothelial cell growth (causing new vessel formation) and increased vascular permeability (causing retinal leakage and exudation).

Low insulin >" Rods and cons insulin dependent " so Macula will need more O2 and blood supply > Neovascularization for more blood supply >cause bleeding from any trauma or even sneeze > develop clot > fibrous tissue > contraction > retinal detachment > blindness

Clinical features of diabetic retinopathy

- Microaneurysms
- Retinal hemorrhages (dot and blot)
- Exudates
- Cotton wool spots
- Venous changes
- Neovascularization (retina and iris)
- Pre-retinal/subhyaloidhaemorrhage
- Vitreous hemorrhage
- Fibrosis/gliosis

The major causes of blindness in diabetic patient
- Cataract
- Retinal detachment
- Retinal bleeding

Prevention

Glycemic, blood pressure and lipid profile control.
Risk factors for retinopathy include early onset and long duration of diabetes, hypertension, poor glycemic control, pregnancy, use of the oral contraceptive pill, smoking, excessive alcohol consumption and evidence ofmicroangiopathy elsewhere, particularly neuropathy and nephropathy.
Hyperglycemia promotes retinal hyperperfusion, so a rapid reduction in blood glucose may cause an initialdeterioration of retinopathy by causing relative ischemia.Blood pressure lowering is of proven benefit in hypertensivepatients, and there may be specific benefit fromangiotensin II receptor antagonists. While the effect ofstatins in retinopathy is limited, clinical trials have suggestedthat fibrate treatment may reduce the requirementfor laser therapy in type-2 diabetes.

Screening

Annual screening for retinopathy is essential in all diabetic patients as the disease is asymptomatic in the early stages, when treatment is most effective.

Management

Severe retinopathy is treated with **retinal photocoagulation (laser treatment**to prevent bleeding**),** which has been shown to reduce severe visual loss by 85% (50% in patients with maculopathy).Vitrectomy may be used in selected cases with advanced diabetic eye disease where visual loss has been caused by recurrent vitreous hemorrhage.

Other causes of visual loss in people with diabetes

Around 50% of visual loss in people with type 2 diabetes results from causes other than diabetic retinopathy. These include cataract, age-related macular degeneration, retinal vein occlusion, retinal arterial occlusion, non-arteriticischemic optic neuropathy and glaucoma.

Diabetic nephropathy

Diabetic nephropathy **is an important cause of morbidity**and mortality, and is now among the most common causes of end-stage renal failure (ESRF) in developed countries. About 30% of patients with type-1 diabetes have developed diabetic nephropathy 20 years after diagnosis,

Risk factors for developing diabetic nephropathy

- Poor control of blood glucose
- Long duration of diabetes
- Presence of other microvascular complications
- Ethnicity (e.g. Asian races, Pima Indians)
- Pre-existing hypertension
- Family history of diabetic nephropathy
- Family history of hypertension

Diabetic patient > increase GFR >microalbuminuria> proteinuria >nephrotic syndrome phase with out treatment during 3-5 years they will develop > end stage renal failure (high urea and creatinine) and they required dialysis .

The first changes coincide with the onset of **microalbuminuria** and include thickening of the glomerular basement membrane and accumulation of matrix material in the mesangium. Subsequently, nodular deposits are characteristic, and glomerulosclerosisworsens as heavy proteinuria develops, until glomeruli are progressively lost and renal function deteriorates

Diagnosis and screening

Microalbuminuria an important indicator of the risk of developing overt diabetic nephropathy,although it is also found in other conditions.Microalbuminuria is therefore most reliable as an indicatorof incipient diabetic nephropathy within the first 10 years of type-1 diabetes, when the majority ofpatients with microalbuminuria will progress to overt nephropathywithin a further 10 years. It is a less reliable predictor of nephropathy in older patients with type-2 diabetes, in whom it may be accounted for by other diseases,although it is a potentially useful marker of an increased risk of macrovascular disease.

Management

If there is evidence of incipient nephropathy, vigorousefforts should be made to reduce the risk of progressionand of cardiovascular disease by:

- Improved control of blood glucose
- Aggressive reduction of blood pressure
- Aggressive cardiovascular risk factor reduction

- □ In type-1 diabetes > ACE inhibitors
- □ In patients with type 2 diabetes > angiotensin II receptor blockers
- □ Non-dihydropyridine calcium antagonists (diltiazem, verapamil) may be suitable alternatives.
- □ Diabetic control becomes difficult as renal impairment progresses. Treatment with metformin should be withdrawn when creatinine is higher than 150 µmol/L (1.7 mg/dL), as the risk of lactic acidosis is increased. Long-actingsulphonylureas should be replaced by shortacting agents that are metabolized rather than excreted.
- □ Renal transplantation can dramatically improve the life of many, and any recurrence of diabetic nephropathy in the allograft is usually too slow to be a serious problem, but associated macrovascular and microvascular disease

elsewhere may still progress. Pancreatic transplantation (generally carried out at the same time as renal transplantation) can produce insulin independence and slow or reverse microvascular disease, but the supply of organs is very limited and this is available to few.

Diabetic neuropathy

This is a relatively early and common complication affecting approximately 30% of diabetic patients. Although in a few patients it can cause severe disability, it is symptomless in the majority. Like retinopathy, it occurs secondary to metabolic disturbance, and prevalence is related to the duration of diabetes and the degree of metabolic control. Although there is some evidence that the central nervous system is affected in long-term diabetes, the clinical impact of diabetes is mainly manifest in the peripheral nervous system.

Diabetic neuropathy: histopathology " mostly catch the long nerves "

• Axonal degeneration of both myelinated and unmyelinatedfibres
Early: axon shrinkage
Later: axonal fragmentation; regeneration
• Thickening of Schwann cell basal lamina> pressure on axon for along time > cut of the axon > loss of sensation
• Patchy, segmental demyelination
• Thickening of basement membrane and microthrombi in intraneural capillaries

Clinical features

Symmetrical sensory polyneuropathy
This is frequently asymptomatic. The most common clinical signs are diminished perception of vibration sensation distally, 'glove-and-stocking' impairment of all other modalities of sensation, and loss of tendon reflexes in the lower limbs. In symptomatic patients, sensory abnormalities are predominant. Symptoms include paresthesia in the feet (and, rarely, in the hands), pain in the lower limbs (dull, aching and/or lancinating, worse at night, and mainly felt on the anterior aspect of the legs), burningsensations in the soles of the feet, cutaneous hyperesthesia and an abnormal gait (commonly wide-based), often associated with a sense of numbness in the feet. Muscle weakness and wasting develop only in advanced cases, but subclinical motor nerve dysfunction is common. Within 10 years of developing overt symptoms of autonomic neuropathy, 30–50% of patients are dead—many from sudden cardiorespiratory arrest, the cause of which is unknown.

Autonomic neuropathy (from step-up)

• Impotence in men (most common presentation)
• Neurogenic bladder—retention, incontinence
• Gastroparesis—chronic nausea and vomiting, early satiety
• Constipation and diarrhea (alternating)
• Postural hypotension

The diabetic foot

The foot is a frequent site for complications in patients with diabetes and for this reason foot care is particularly important.
Tissue necrosis in the feet is a common reason for hospital admission in diabetic patients. Such admissions tend to be prolonged and may end with amputation.

Etiology

Foot ulceration occurs as a result of trauma (often trivial) in the presence of neuropathy and/or peripheral vascular disease, with infection occurring as a secondary phenomenon following disruption of the protective epidermis. Most ulcers develop at the siteof a plaque of callus skin beneath which tissue necrosis occurs and eventually breaks through to the surface

21.51 Clinical features of the diabetic foot

	Neuropathy	Ischaemia
Symptoms	None Paraesthesiae Pain Numbness	None Claudication Rest pain
Structural damage	Ulcer Sepsis Abscess Osteomyelitis Digital gangrene Charcot joint	Ulcer Sepsis Gangrene

Management

Effective treatment of local infection with appropriate antibiotics is essential, and may have to be continued for protracted periods; osteomyelitis may be extremely difficult to eradicate. Charcot neuroarthropathy with disorganization of joints may cause serious deformity. Angiography may be necessary if the foot is ischemic or ulcers are very slow to heal. Measures to improve glycemic control may also promote healing. Amputation may be unavoidable if there is extensive tissue and/or bony destruction or intractable ischemic pain at rest in a limb in which vascular reconstruction has failed or is impossible due to extensive large blood vessel disease.

Specific treatment of chronic diabetic complications

1. Macrovascular disease—treatment involves reduction of risk factors (e.g., BP reduction, lipid-lowering agents, smoking cessation, exercise), a daily aspirin(if not contraindicated), and strict glycemic control.
2. Nephropathy—ACE inhibitors, benefits of which include:
a. Slow progression of microalbuminuria to proteinuria
b. Slow decline of GFR
3. Retinopathy—Treatment involves referral to an ophthalmologist and possible photocoagulation.
4. Neuropathy—Treatment is complex. Pharmacologic agents that may be helpful include NSAIDs, tricyclic antidepressants, and gabapentin. For gastroparesis, apromotility agent such as metoclopramide can be helpful, in addition to exerciseand a low-fat diet.
5. Diabetic foot—The best treatment is prevention: regular foot care, regular**podiatrist*** visits. Amputation is a last resort.***(Podiatry or podiatric medicine is a branch of medicine devoted to the study of diagnosis, medical and surgical treatment of disorders of the foot, ankle, and lower extremity.)**

Summary:

- In type-2 diabetes, small amounts of insulin fight back the ketoacidosis.
- Neuropathy is the most common complication and the highest in morbidity. Vasculopathy is the highest in mortality.
- Type-1 diabetes is the leading cause of blindness, leading cause of renal failure and leading cause of death among diabetic patients.
- In neuropathy, the pathophysiology occurs in the schwann cells which depend on insulin, in contrast to the other neurological tissue which uptakes the glucose immediately.
- In retinopathy, neovascularization of fragile arteries happen and these arteries are susceptible to bleed from any minor trauma.
- In vasculopathy, coronary artery disease (CAD) is the most common among the three manifestations (Cerebrovascular accident, coronary artery disease and peripheral artery disease)
    - In a diabetic with coronary artery disease, there is decrease in energy (due to loss of insulin) and the cardiac muscles get fatigued, hence ischemia.
    - Most of the diabetic patients with (CAD) come with more than one (+1) vessel disease because they do not feel the pain.
    - Cerebrovascular accident is the 2nd most common manifestation.
- Once the diabetes is controlled, the risk of developing complications decreases. Yet, one can complain of nothing with poor control.
- Diabetics usually come with macrovascular calcification, and it is the opposite in non-diabetics.

Q: 50-year-old obese female is taking oral hypoglycemic agents. While being treated for an upper respiratory infection, she develops lethargy and is brought to the emergency room. On physical

exam, there is no focal neurologic finding or neck rigidity. Laboratory results are as follows:

Na^+: 134 meq/L K^+: 4.0 meq/L HCO_3: 25 meq/L

Glucose: 900 mg/dL BUN: 84 mg/dL Creatinine: 3.0 mg/dL

BP: 120/80 sitting, 105/65 lying down

Which of the following is the most likely cause of this patient's coma?

a. Diabetic ketoacidosis

b. Hyperosmolar coma

c. Inappropriate ADH

d. Bacterial meningitis

The Answer is B. This obese patient on oral hypoglycemics has developed hyperglycemia and lethargy during an upper respiratory infection. Hyperosmolar nonketotic states that occur in type 2 diabetes can be fatal. When severe hyperglycemia and dehydration increase serum osmolarity above 380 mOsm/L, lethargy or coma occurs. Serum osmolarity is measured by the formula:

$$\frac{\text{Plasma glucose}}{18} + 2\,(\text{serum } Na^+ + K^+) + \frac{\text{blood urea nitrogen}}{2.8}$$

This patient's serum osmolality is as follows:

$$\frac{900}{18} + 2\,(138) + \frac{84}{2.8} = 50 + 276 + 30 = 356$$

Thus the serum osmolality is greater than 350 mOsm/kg. As can be seen from the equation, osmolarity depends mostly on the concentration of sodium. Serum osmolarity will rise significantly when dehydration prevents the dilution of serum sodium that might otherwise occur with hyperglycemia. Hyperosmolarity reflects both hyperglycemia and severe dehydration with hypernatremia. The serum bicarbonate is too high to be consistent with diabetic ketoacidosis. The hyponatremia is related to hyperglycemia. SIADH could not be diagnosed in this clinical setting. Patients with SIADH are not dehydrated but have an inappropriate excretion of ADH that leads to hyponatremia and water retention. The patient's diabetes likely went out of control due to infection. There is no clinical evidence for meningitis.