

Pathophysiology of Diabetes

PHCL 415
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Learning Objectives

- Define diabetes mellitus
- Describe differences in epidemiology of type 1 and type 2
- Understand different types of DM including type 1, type 2 & GDM
- Compare & contrast type 1 and type 2 diabetes presentation, onset, progression, and pathophysiology
- List the plasma glucose levels that diagnose a patient with: impaired fasting glucose, impaired glucose tolerance, or diabetes mellitus & GDM

Outline

- Introduction
- Epidemiology
- Causes/Classification
- Pathophysiology
- Manifestations (signs and symptoms)
- Complications
- Diagnosis

Introduction

Introduction

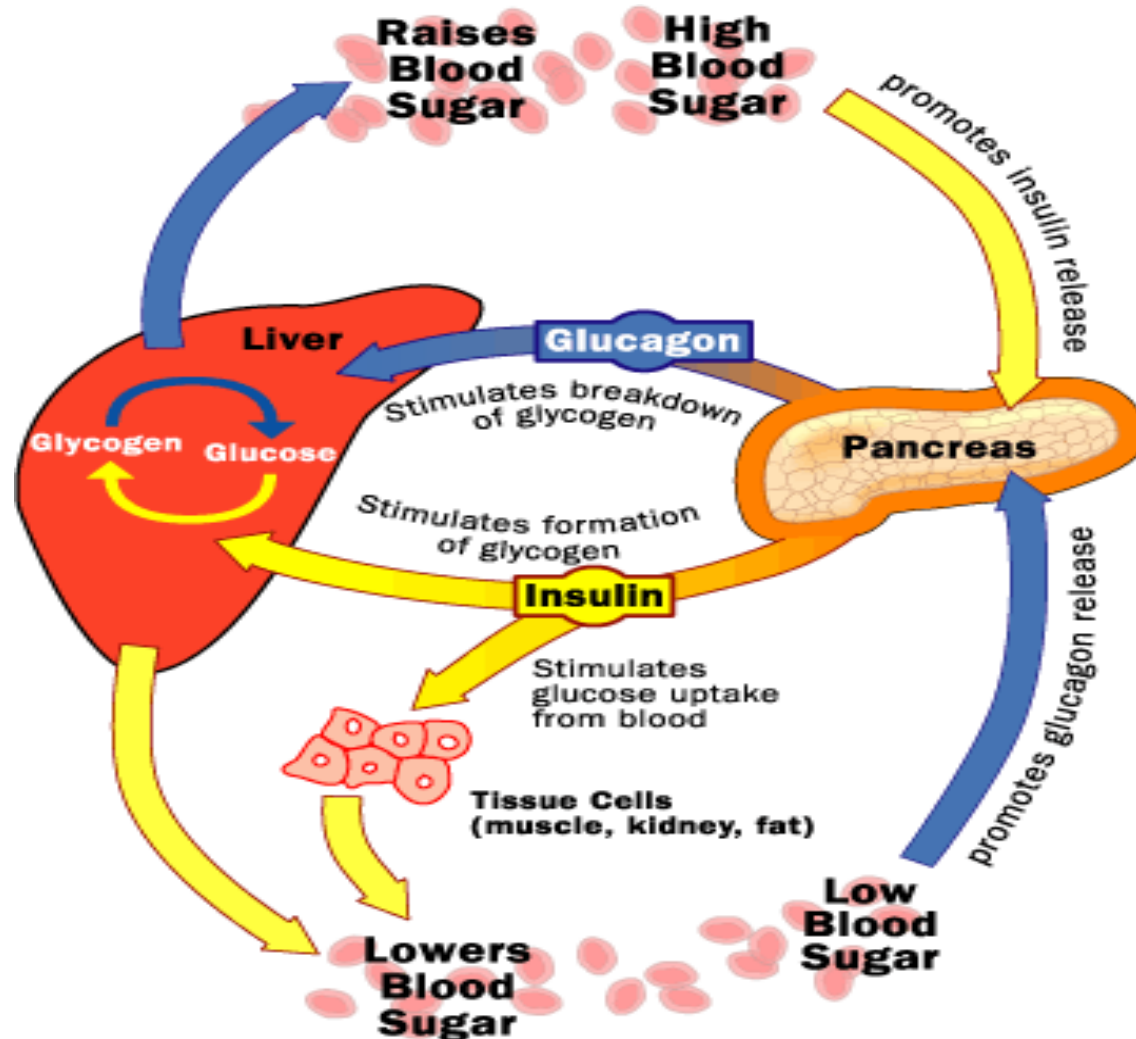
- Glucose homeostasis
- Liver & pancreas
- Direct effects of insulin
- Definitions

Glucose Homeostasis

Glycogenolysis & Gluconeogenesis

- Glycogenolysis: Catabolism of glycogen
- Gluconeogenesis: Production of glucose from carbohydrates or proteins

Liver & Pancreas



Directs Effects of Insulin

- Glucose metabolism
- Lipoprotein metabolism
- Ketone metabolism
- Protein metabolism

Directs Effects of Insulin

- Glucose metabolism
- Lipoprotein metabolism
- Ketone metabolism
- Protein metabolism

Glucose Metabolism

Major Metabolic Effects of Insulin	Consequences of Insulin Deficiency
<ul style="list-style-type: none">■ Stimulates glucose uptake into muscle and adipose cells■ Inhibits hepatic glucose production	<ul style="list-style-type: none">■ Hyperglycemia → osmotic diuresis and dehydration

Lipoprotein Metabolism

Major Metabolic Effects of Insulin	Consequences of Insulin Deficiency
<ul style="list-style-type: none">■ Inhibits breakdown of triglycerides (lipolysis) in adipose tissue	<ul style="list-style-type: none">■ Elevated FFA levels

Ketone Metabolism

Major Metabolic Effects of Insulin	Consequences of Insulin Deficiency
<ul style="list-style-type: none">■ Inhibits ketogenesis■ Ketogenesis: is the process by which ketone bodies are produced as a result of fatty acid breakdown.	<ul style="list-style-type: none">■ Ketoacidosis

Protein Metabolism

Major Metabolic Effects of Insulin	Consequences of Insulin Deficiency
<ul style="list-style-type: none">■ Stimulates amino acid uptake & protein synthesis■ Inhibits protein degradation■ Regulates gene transcription	<ul style="list-style-type: none">■ Muscle wasting■ Others

Diabetes Mellitus (DM)

- DM is a group of metabolic disorders characterized by hyperglycemia
- It is associated with abnormalities in carbohydrate, fat, & protein metabolism
- Results in chronic complications including microvascular, macrovascular, & neuropathic disorders

Epidemiology

Diabetes Mellitus (DM)

- Typical **type 1 DM** is an autoimmune disorder developing in childhood or early adulthood, although some latent forms do occur
- **Type 1 DM** accounts for 5% to 10% of all cases of DM & is likely initiated by the exposure of a genetically susceptible individual to an environmental agent

Diabetes Mellitus (DM)

- **Type 2 DM** accounts for as much as 90% of all cases of DM
- Risk factors for the development of type 2 DM:
 - Family history
 - Obesity
 - Habitual physical inactivity
 - Race or ethnicity
 - Hypertension
 - Dyslipidemia
 - history of gestational DM
 - Polycystic ovary disease

Diabetes Mellitus (DM)

- The prevalence of **type 2 DM** increases with age
- It is more common in women than in men
- Although the prevalence of **type 2 DM** increases with age, the disorder is increasingly being recognized in adolescence
- The increase in adolescent **type 2 DM** is related to an increase in adiposity & sedentary lifestyle, in addition to an inheritable predisposition

Diabetes Mellitus (DM)

- Gestational diabetes mellitus (**GDM**) complicates roughly 7% of all pregnancies
- Most women will return to normoglycemia postpartum
- 30% to 50% will develop type 2 DM or glucose intolerance later in life

Classification

Classification

- Type I DM
- Type II DM
- Gestational DM
- Other specific types of diabetes due to other causes, e.g., genetic defects in cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis)

Type I DM

- Known as 'juvenile', or Insulin-dependent DM (**IDDM**)
- Accounts for 5% - 10% of total diabetes cases
- Onset is between 8-14 yrs old usually presenting with ketosis
- Regarded as an auto-immune disease (Antibodies to islet cells &/or insulin)
- Gradual loss of beta cell function until no longer able to synthesize adequate insulin to control blood sugar
- Presenting symptoms are polydipsia, polyuria, polyphagia & weight loss

Type I DM

- Patients are most often lean
- Patients must rely on exogenous sources of insulin
- ***Honey-moon phase:***
 - After weeks of diagnosis patients have period of remission (decrease in blood glucose concentration)
 - Endogenous insulin secretion recovers temporarily
 - May last for weeks, months or a year

Type II DM

- Formerly known as “adult-onset” or Non-insulin dependent diabetes mellitus (**NIDDM**)
- 90% of total cases
- Very strong genetic component
- 80% with Type 2 are obese
- Defect in insulin secretion:
 - Tissue resistance to insulin
 - Increase in hepatic glucose production



Type II DM

- Usually associated with a variety of disorders:

➤ Obesity

➤ Atherosclerosis

➤ Hyperlipidemia



Metabolic syndrome or
syndrome X

Gestational DM (GDM)

- Affect around 7% of pregnancies
- Any carbohydrate intolerance with first recognition during pregnancy
- Risk on fetus:
 - Neonatal death
 - Macrosomia (infant weight > 9 pounds)
- Risk on mother:
 - Greater chance for cesarean section
 - HTN

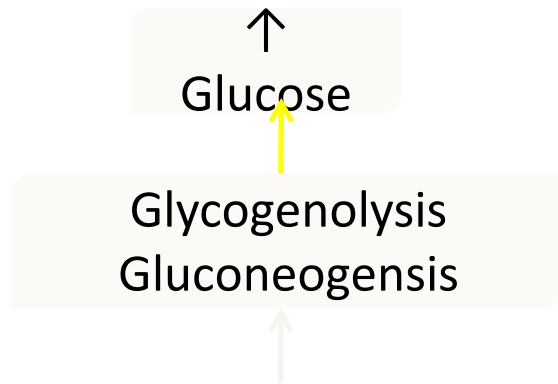
Pathophysiology

Pathophysiology

- Carbohydrate metabolism
- Hyperglycemia
- Pathogenesis of type 1 DM
- Pathogenesis of type 2 DM:
 - Normal insulin action
 - Impaired insulin secretion
 - Sites of insulin resistance
 - Metabolic syndrome

Carbohydrate Metabolism

Postprandial Metabolism



Counterregulatory hormones release

Glucagon
Epinephrine
Cortisol
Growth hormone

Insulin release (anabolism)

Turns on

Glucose → Glycogen

AA → Protein

FFA → TG

Shuts off

Fasting Metabolism

Hyperglycemia

- Hyperglycemia in all cases is due to a functional deficiency of insulin action
- Deficient insulin action can be due to a decrease in insulin secretion by the cells of the pancreas, a decreased response to insulin by target tissues (insulin resistance), or an increase in the counterregulatory hormones that oppose the effects of insulin
- The relative contributions of each of these three factors not only form the basis of classification of this disorder into subtypes but also help to explain the characteristic clinical presentations of each subtype

Pathogenesis of Type 1 DM

- Characterized by an absolute deficiency of pancreatic -cell function
- Result of an immune-mediated destruction of pancreatic cells, but rare unknown or idiopathic processes can contribute

Pathogenesis of Type 1 DM

- Four main features
 1. A long preclinical period marked by the presence of immune markers when β -cell destruction is thought to occur
 2. Hyperglycemia when 80% to 90% of cells are destroyed
 3. Transient remission (the so-called honeymoon phase)
 4. Established disease with associated risks for complications & death
- Unknown is whether there is one or more inciting factors (e.g., cow's milk, or viral, dietary, or other environmental exposure) that initiate the autoimmune process

Pathogenesis of Type 1 DM

- The autoimmune process is mediated by macrophages & T lymphocytes with circulating autoantibodies to various -cell antigens
- The most commonly detected antibody associated with type 1 DM is the islet cell antibody
- Other antibodies include insulin autoantibodies, antibodies directed against glutamic acid decarboxylase, insulin antibodies against islet tyrosine phosphatase, & others
- More than 90% of newly diagnosed persons with type 1 DM have one or another of these antibodies, as will 3.5% to 4% of unaffected first-degree relatives.

Pathogenesis of Type 1 DM

- Destruction of pancreatic β -cell function causes hyperglycemia because of an absolute deficiency of both insulin & amylin
- Insulin lowers blood glucose by a variety of mechanisms:
 - Stimulation of tissue glucose uptake
 - Suppression of glucose production by the liver
 - Suppression of free fatty acid release from fat cells

Pathogenesis of Type 1 DM

- The suppression of free fatty acids plays an important role in glucose homeostasis
- Increased levels of free fatty acids inhibit the uptake of glucose by muscle & stimulate hepatic gluconeogenesis
- Amylin, a glucoregulatory peptide hormone co-secreted with insulin, plays a role in lowering blood glucose by slowing gastric emptying, & suppressing glucagon output from pancreatic cells
- In type 1 DM amylin production, caused by β -cell destruction, is very low

Pathogenesis of Type 2 DM

- Normal Insulin action
- Impaired Insulin secretion
- Sites of Insulin resistance
- Metabolic Syndrome

Pathogenesis of Type 2 DM

Normal Insulin actions

“Fasting State”

- 75% of body glucose disposal takes place in non–insulin-dependent tissues: the brain & splanchnic tissues (liver & gastrointestinal [GI] tissues)
- The remaining 25% of glucose metabolism takes place in muscle, which is dependent on insulin
- 85% of glucose production is derived from the liver, & the remaining amount is produced by the kidney
- Glucagon, produced by pancreatic cells, is secreted to oppose the action of insulin & stimulate hepatic glucose production. Thus, glucagon prevents hypoglycemia

Pathogenesis of Type 2 DM

Normal Insulin actions

“Fed State”

- Carbohydrate ingestion increases the plasma glucose concentration and stimulates insulin release from the pancreatic cells
- The resultant hyperinsulinemia (1) suppresses hepatic glucose production & (2) stimulates glucose uptake by peripheral tissues
- The majority (~80%–85%) of glucose that is taken up by peripheral tissues is disposed of in muscle
- Glucagon is suppressed

Pathogenesis of Type 2 DM

Normal Insulin actions

- Although fat tissue is responsible for only a small amount of total body glucose disposal, it plays a very important role in the maintenance of total body glucose homeostasis
- Small increments in the plasma insulin concentration exert a potent antilipolytic effect, leading to a marked reduction in the plasma free fatty acid (FFA) level
- Decline in FFA increases glucose uptake in muscle & reduces hepatic glucose production
- Thus a decrease in FFA lowers plasma glucose by decreasing its production & enhancing the uptake in muscle

Pathogenesis of Type 2 DM

- Type 2 diabetic individuals are characterized by:
 1. Defects in insulin secretion
 2. Insulin resistance involving muscle, liver, and the adipocyte

Pathogenesis of Type 2 DM

- Whether the primary lesion in Type 2 DM is insulin resistance or defective cell insulin secretion, continues to be debated
- Several decades before the onset of clinical diabetes, insulin resistance & high insulin levels are present
- This has led researchers to hypothesize that insulin resistance could be the primary lesion, resulting in a compensatory increase in insulin secretion that ultimately cannot be maintained by the pancreas
- When the pancreas becomes "exhausted" and cannot keep up with insulin demands, clinical diabetes results.

Pathogenesis of Type 2 DM

Impaired Insulin Secretion

- The pancreas in people with a normal-functioning cell is able to adjust its secretion of insulin to maintain normal glucose tolerance
- Thus in nondiabetic individuals, insulin is increased in proportion to the severity of the insulin resistance, & glucose tolerance remains normal
- Impaired insulin secretion is a uniform finding in type 2 DM patients

Pathogenesis of Type 2 DM

Sites of Insulin Resistance

“Liver”

- Following glucose ingestion, insulin is secreted into the portal vein & carried to the liver, where it suppresses glucagon secretion & reduces hepatic glucose output
- Type 2 DM patients fail to suppress glucagon in response to a meal & can even have a paradoxical rise in glucagon levels
- Thus, hepatic insulin resistance & hyperglucagonemia result in continued production of glucose by the liver
- Type 2 DM patients have 2 sources of glucose in the postprandial state, one from the diet & one from continued glucose production from the liver

Pathogenesis of Type 2 DM

Sites of Insulin Resistance

“Peripheral (Muscle)”

- Muscle is the major site of glucose disposal & approximately 80% of total body glucose uptake occurs in skeletal muscle
- In response to a physiologic increase in plasma insulin concentration, muscle glucose uptake increases linearly
- In contrast, in type 2 diabetic subjects, the onset of insulin action is delayed for ~40 minutes, & the ability of insulin to stimulate glucose uptake is reduced by 50%
- Therefore the primary site of insulin resistance in type 2 diabetic subjects resides in muscle tissue

Pathogenesis of Type 2 DM

Sites of Insulin Resistance

“Peripheral (Adipocy)”

- In obese nondiabetic & DM humans, FFA levels are increased & fail to suppress normally after glucose ingestion
- FFAs are stored as triglycerides in adipocytes & serve as an important energy source during conditions of fasting
- Insulin is a potent inhibitor of lipolysis, & restrains the release of FFAs from the adipocyte by inhibiting the hormone-sensitive lipase enzyme

Pathogenesis of Type 2 DM

Sites of Insulin Resistance

“Peripheral (Adipocy)”

- It is now recognized that chronically elevated plasma FFA concentrations can lead to insulin resistance in muscle & liver & impair insulin secretion
- In addition to FFAs that circulate in plasma in increased amounts, type 2 diabetic & obese nondiabetic individuals have increased stores of triglycerides in muscle & liver
- The increased fat content correlates closely with the presence of insulin resistance in these tissues

Pathogenesis of Type 2 DM

Sites of Insulin Resistance

- Insulin resistance involving both muscle & liver are characteristic features of the glucose intolerance in type 2 diabetic individuals
- In the basal state, the liver represents a major site of insulin resistance, and this is reflected by overproduction of glucose
- This accelerated rate of hepatic glucose output is the primary determinant of the elevated FPG concentration in type 2 diabetic individuals

Pathogenesis of Type 2 DM

Sites of Insulin Resistance

- In the fed state, both decreased muscle glucose uptake & impaired suppression of hepatic glucose production contribute to the insulin resistance
- In obese individuals & in the majority (>80%) of type 2 diabetic subjects, there is an expanded fat cell mass, & the adipocytes are resistant to the antilipolytic effects of insulin

Pathogenesis of Type 2 DM

Metabolic Syndrome

- The association of insulin resistance with cardiovascular risk factors including hyperinsulinemia, hypertension, abdominal obesity, dyslipidemia, & coagulation abnormalities has been referred to by a variety of names including "the insulin resistance syndrome," & "the metabolic syndrome"
- Since the description of the "insulin resistance syndrome" by Reaven in 1988 the number of associated factors has continued to grow

Pathogenesis of Type 2 DM

Metabolic Syndrome

Risk Factor	Defining Level
Abdominal obesity	Waist circumference
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglycerides	150 mg/dL
High-density–lipoprotein C	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	130/85 mm Hg
Fasting glucose	110 mg/dL

NCEP ATP III: Five Components of the Metabolic Syndrome (Individuals Having at Least Three Components Meet the Criteria for Diagnosis)

Manifestations

Clinical Manifestations

Type 1 DM

- Clinical presentations of type 1 & 2 DM are very different
- Autoimmune type 1 DM can occur at any age
- 75% will develop the disorder before age 20 years, the remaining 25%, develop the disease as adults
- Individuals with type 1 DM are often **thin** & are **prone to develop diabetic ketoacidosis** if insulin is withheld, or under conditions of severe stress with an excess of counterregulatory hormones

Clinical Manifestations

Type 1 DM

- 20-40% of patients with type 1 DM present with diabetic ketoacidosis after several days of **polyuria, polydipsia, polyphagia, & weight loss**
- Newly diagnosed type 1 DM often have a small amount of residual pancreatic -cell function, & enter a "honeymoon" phase, their blood glucose concentrations are relatively easy to control & small amounts of insulin are needed
- Once this residual insulin secretion wanes, the patients are completely insulin deficient & tend to have more labile glycemia

Clinical Manifestations

Type 2 DM

- Patients with type 2 DM often present without symptoms
- Usually complications tell us that they may have had type 2 DM for several years
- Often these patients are diagnosed secondary to unrelated blood testing
- Lethargy, polyuria, nocturia, & polydipsia can be seen at diagnosis in type 2 diabetes
- Significant weight loss at diagnosis is less common

Clinical Manifestations

Characteristic	Type 1 DM	Type 2 DM
Age	<30 years	>30 years
Onset	Abrupt	Gradual
Body habitus	Lean	Obese/history of obesity
Insulin resistance	Absent	Present
Autoantibodies	Often present	Rarely present
Symptoms	Symptomatic	Often asymptomatic
Ketones at diagnosis	Present	Absent
Need for insulin therapy	Immediate	Years after diagnosis
Acute complications	Diabetic ketoacidosis	Hyperosmolar hyperglycemic state
Microvascular complications at diagnosis	No	Common
Macrovascular complications at or before diagnosis	Rare	Common

Complication

Complications

- Acute
- Chronic:
 - Macrovascular
 - Microvascular

Complications

Acute Complications

“Hyperglycemia”

- When elevated glucose levels exceed the renal threshold for reabsorption of glucose, glucosuria results
- This causes an osmotic diuresis manifested clinically by polyuria, including nocturia. Dehydration results, stimulating thirst that results in polydipsia. A significant loss of calories can result from glucosuria
- Polyphagia also accompanies uncontrolled hyperglycemia

Complications

Acute Complications

“Hyperglycemia”

- The 3 "polys" of diabetes polyuria, polydipsia, & polyphagia are common in both type 1 & symptomatic type 2 patients
- Weight loss can also occur as a result of both dehydration & loss of calories in the urine
- Severe weight loss is most likely to occur in type 1 DM & is due to both caloric loss and muscle wasting
- Increased protein catabolism also contributes to the growth failure seen in children with Type 1 DM

Complications

Acute Complications

“Diabetic Ketoacidosis”

- A profound loss of insulin activity leads also to ketogenesis
- In the absence of insulin, lipolysis is stimulated, providing FFA that are converted to ketone bodies in the liver
- Profound hyperglycemia and ketosis (diabetic ketoacidosis) occur in Type 1 diabetics, individuals who lack endogenous insulin
- Diabetic ketoacidosis can occur in type 2 DM, particularly during infections, severe trauma, or stress that increase levels of counterregulatory hormones

Complications

Acute Complications

“Diabetic Ketoacidosis”

- Na^+ is lost in addition to water during the osmotic diuresis accompanying diabetic ketoacidosis
- Serum levels of Na^+ are usually low owing to the osmotic activity of the elevated glucose, which draws water into the extracellular space and in that way decreases the Na^+ concentration
- Total body stores of K^+ are also depleted by diuresis and vomiting. However, acidosis & elevated glucose levels cause a shift of K^+ out of cells, thus maintaining normal or even elevated serum K^+ levels until acidosis & hyperglycemia are corrected

Complications

Acute Complications

“Diabetic Ketoacidosis”

- With administration of insulin & correction of acidosis, serum K⁺ falls as K⁺ moves back into cells
- Without treatment, K⁺ can fall to dangerously low levels, leading to potentially lethal cardiac arrhythmias
- Therefore, K⁺ supplementation is routinely given in the treatment of diabetic ketoacidosis

Complications

Acute Complications

“Diabetic Ketoacidosis”

- Nausea & vomiting often accompany diabetic ketoacidosis, contributing to further dehydration
- Abdominal pain, present in 30% of patients
- Leukocytosis is frequently present and does not necessarily indicate the presence of infection. However, because infections can precipitate diabetic ketoacidosis in type 1 DM & type 2 DM, other manifestations of infection should be sought, such as fever, a finding that cannot be attributed to diabetic ketoacidosis

Complications

Acute Complications

“Hyperosmolar Coma”

- Severe hyperosmolar states in the absence of ketosis can occur in Type 2 DM
- These episodes are precipitated by decreased fluid intake
- The mechanisms underlying the development of hyperosmolality and hyperosmolar coma are the same as in diabetic ketoacidosis
- Because only minimal levels of insulin activity are required to suppress lipolysis, these individuals have sufficient insulin to prevent the ketogenesis that results from increased fatty acid flux

Complications

Acute Complications

“Hyperosmolar Coma”

- Because of the absence of ketoacidosis & its symptoms, patients often present later and, therefore, have more profound hyperglycemia and dehydration
- Glucose levels often range from 800–2400 mg/dL. Therefore, the effective osmolality exceeds 340 mOsm/L more frequently in these patients than in those presenting with diabetic ketoacidosis, resulting in a higher incidence of coma

Complications

Chronic Complications: 1)Microvascular

“Retinopathy”

- Diabetes is the leading cause of new blindness among adults
- Diabetic retinopathy, present after 20 years in >95% with type 1 DM & 60% with type 2 DM
- Occurs in two distinct stages: nonproliferative and proliferative

Long Term Complications

Microvascular disease

- Ocular complications
- Nephropathy
- Neuropathy

Macrovascular disease

- Coronary heart disease (leading cause of death in type 2 DM)
- Stroke
- Peripheral vascular disease (diabetes is the leading cause of non-traumatic amputations)

Complications

Chronic Complications: 1)Microvascular

“Retinopathy”

- Hyperglycemia-induced intramural pericyte death & thickening of the basement membrane lead to incompetence of the vascular walls
- These damages change the formation of blood-retinal barrier & make the retinal blood vessel more permeable
- During the initial stage, nonproliferative diabetic retinopathy (NPDR), most people do not notice any change in their vision

Complications

Chronic Complications: 1)Microvascular

“Retinopathy”

- Some people develop a condition called macular edema. It occurs when the damaged blood vessels leak fluid & lipids onto the macula, the part of the retina that lets us see detail. The fluid makes the macula swell, which blurs vision
- Nonproliferative diabetic retinopathy shows up as cotton wool spots, or microvascular abnormalities or as superficial retinal hemorrhages

Complications

Chronic Complications: 1)Microvascular

“Retinopathy”

- As the disease progresses, severe nonproliferative diabetic retinopathy enters an advanced, or proliferative, stage
- The lack of oxygen in the retina causes fragile, new, blood vessels to grow along the retina
- Without timely treatment, these new blood vessels can bleed, cloud vision, & destroy the retina
- Advanced proliferative diabetic retinopathy (PDR) can remain asymptomatic for a very long time, and so should be monitored closely with regular checkups

Complications

Chronic Complications: 1)Microvascular

“Retinopathy”



Complications

Chronic Complications: 1)Microvascular

“Retinopathy”



Normal vision

Complications

Chronic Complications: 1)Microvascular

“Retinopathy”



The same view with diabetic retinopathy

Complications

Chronic Complications: 1)Microvascular

“Nephropathy”

- More than 50% of end-stage renal disease requiring kidney dialysis or transplantation is due to diabetes
- Although end-stage renal disease occurs more frequently in type 1 than in type 2 DM (35% vs. 20% after 20 years), type 2 DM accounts for more than half of the diabetic population with end-stage renal disease because of its greater prevalence

Complications

Chronic Complications: 1)Microvascular

“Nephropathy”

- Diabetic nephropathy results primarily from disordered glomerular function
- Basement membranes of the glomerular capillaries are thickened and can obliterate the vessels
- The mesangium surrounding the glomerular vessels is increased owing to the deposition of basement membrane-like material

Complications

Chronic Complications: 1)Microvascular

“Nephropathy”

- Early in the course of the disease, the histologic changes in renal glomeruli are accompanied by microalbuminuria, a urinary loss of albumin that cannot be detected by routine urinalysis dipstick methods
- Albuminuria is thought to be due to a decrease in the heparan sulfate content of the thickened glomerular capillary basement membrane. Heparan sulfate inhibits the filtration of proteins, such as albumin, through the basement membrane; its loss allows for increased albumin filtration

Complications

Chronic Complications: 1)Microvascular

“Nephropathy”

- If glomerular lesions worsen, proteinuria increases & overt nephropathy develops
- Diabetic nephropathy is defined clinically by the presence of more than 300 mg of urinary protein per day, an amount that can be detected by routine urinalysis
- In diabetic nephropathy (unlike other renal diseases), proteinuria continues to increase as renal function decreases. Therefore, end-stage renal disease is preceded by massive, nephrotic-range proteinuria (> 4 g/d)

Complications

Chronic Complications: 1)Microvascular

“Nephropathy”

- The presence of hypertension speeds this process
- Although type 2 DM often already have hypertension at the time of diagnosis, type 1 patients usually do not develop hypertension until after the onset of nephropathy
- In both cases, hypertension worsens as renal function deteriorates. Therefore, control of hypertension is critical in preventing the progression of diabetic nephropathy

Complications

Chronic Complications: 1)Microvascular

“Neuropathy”

- Neuropathy occurs in about 60% of both type 1 & type 2 diabetics & is a major cause of morbidity
- Severe peripheral neuropathy coupled with abnormalities in immune function likely contribute to the high rate of lower extremity amputations among patients with diabetes

Complications

Chronic Complications: 2) Macrovascular

- Atherosclerotic macrovascular disease occurs with increased frequency in diabetes, resulting in an increased incidence of myocardial infarction, stroke, & gangrene of the lower extremities
- Although macrovascular disease accounts for significant morbidity and mortality in both types of diabetes, the effects of large-vessel disease are particularly devastating in type 2 DM & are responsible for approximately 75% of deaths
- The protective effect of gender is lost in women with diabetes; their risk of atherosclerosis is equal to that of men

Complications

Chronic Complications: 2) Macrovascular

- Reasons for the increased risk of atherosclerosis in diabetes
 1. The incidence of traditional risk factors, such as hypertension & hyperlipidemia, is increased (50% & 30% incidence at diagnosis, respectively)
 2. Diabetes itself is an independent risk factor for atherosclerosis
 3. Diabetes appears to synergize with other known risk factors to increase atherosclerosis
- The elimination of other risk factors, therefore, can greatly reduce the risk of atherosclerosis in diabetes

Complications

Chronic Complications: 2) Macrovascular

“Foot Ulcers”

- Diabetic foot ulcers occur in 15% of diabetics
- Result in amputations in 2%
- Associated with high mortality (50% by 3 years)

Complications

Chronic Complications

“Foot Ulcers”

- Risk factors for ulcer development include:
 1. Increased in insensitve injuries due to symmetric polyneuropathy (in 75–90% of diabetics with foot ulcers)
 2. Macrovascular disease (present in 30–40% with foot ulcers)
 3. Infections caused by alterations in neutrophil function & vascular insufficiency
 4. Faulty wound healing caused by unknown factors

Complications

Chronic Complications

“Infections”

- Neutrophil chemotaxis & phagocytosis are defective in poorly controlled diabetes
- Cell-mediated immunity also is abnormal
- In addition, vascular lesions can hinder blood flow, preventing inflammatory cells from reaching wounds (eg, foot ulcers) or other possible sites of infection

Complications

Chronic Complications

“Infections”

- Therefore, individuals with diabetes are more prone to develop infections & may have more severe infections
- As a result, certain common infections (eg, candidal infections, periodontal disease) occur more frequently in diabetics
- A number of unusual infections also are seen in diabetics (ie, necrotizing papillitis, & malignant otitis externa caused by *Pseudomonas aeruginosa*)

Diagnosis

Diagnosis

- First look at S & S
- Fasting blood glucose
- Random blood glucose
- OGTT (oral glucose tolerance test)
- Pre-Diabetes
- How to differ between type I & II DM?
- GDM diagnosis

Diagnosis

Criteria for the diagnosis of diabetes (Type 1 or type 2)

1 FPG \geq 126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h

OR

2 Symptoms of hyperglycemia & a casual plasma glucose 200 mg/dl (11.1 mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of hyperglycemia include polyuria, polydipsia, & unexplained weight loss

OR

3 2-h plasma glucose 200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water

Diagnosis

- The ADA recommends using the fasting glucose test as the principal tool for the diagnosis of DM in non-pregnant adults
- These criteria should be confirmed by repeat testing on a different day
- Although the OGTT is not recommended for routine clinical use, it may be useful for further evaluation of patients in whom diabetes is still strongly suspected but who have normal FPG or impaired fasting glucose (IFG)

Diagnosis

Diagnosis of Pre-Diabetes

- Hyperglycemia not sufficient to meet the diagnostic criteria for diabetes is categorized as either IFG or impaired glucose tolerance (IGT), depending on whether it is identified through the FPG or the OGTT:
- IFG = FPG 100 mg/dL - 125 mg/dL
- IGT = 2-h plasma glucose 140 mg/dL - 199 mg/dL
- IFG & IGT have been officially termed "pre-diabetes"

Type I OR Type II DM?

- Young (<30), lean & with S & S and high blood glucose usually type I
- Ketonuria strongly support the diagnosis of type I DM
- 8 – 45% of children diagnosed with DM have type II DM
- Obesity usually goes with type II DM
- In type II DM there is a strong family history
- C-peptide test: if (+) type II DM, if (-) type I DM Why?

GDM

- Women at very high risk for GDM should be screened as soon as possible after the confirmation of pregnancy
- Criteria for very high risk are:
 - Severe obesity
 - History of GDM or delivery of large-for-gestational-age infant
 - Presence of glycosuria
 - Diagnosis of PCOS
 - Strong family history of type 2 diabetes
- If not found to have diabetes early in pregnancy, should undergo GDM testing at 24–28 weeks of gestation

GDM

- Low risk status, which does not require GDM screening, is defined as women with ***all of the following*** characteristics:
 - Age 25 years
 - Weight normal before pregnancy
 - Member of an ethnic group with a low prevalence of DM
 - No known diabetes in first-degree relatives
 - No history of abnormal glucose tolerance
 - No history of poor obstetrical outcome

GDM

- A diagnosis of GDM requires at least two of the following plasma glucose values:
 - Fasting: ≥ 95 mg/dl (≥ 5.3 mmol/l)
 - 1 h: ≥ 180 mg/dl (≥ 10.0 mmol/l)
 - 2 h: ≥ 155 mg/dl (≥ 8.6 mmol/l)
 - 3 h: ≥ 140 mg/dl (≥ 7.8 mmol/l)

References

- Pharmacotherapy: A Pathophysiologic Approach, 7e
- Pathophysiology of Disease: An Introduction to Clinical Medicine, 6e
- Applied Therapeutics: The Clinical Use of Drugs, 9e

Thank You