ENDOCRINE PANCREAS

Kenneth Alonso, MD, FACP

Pancreas

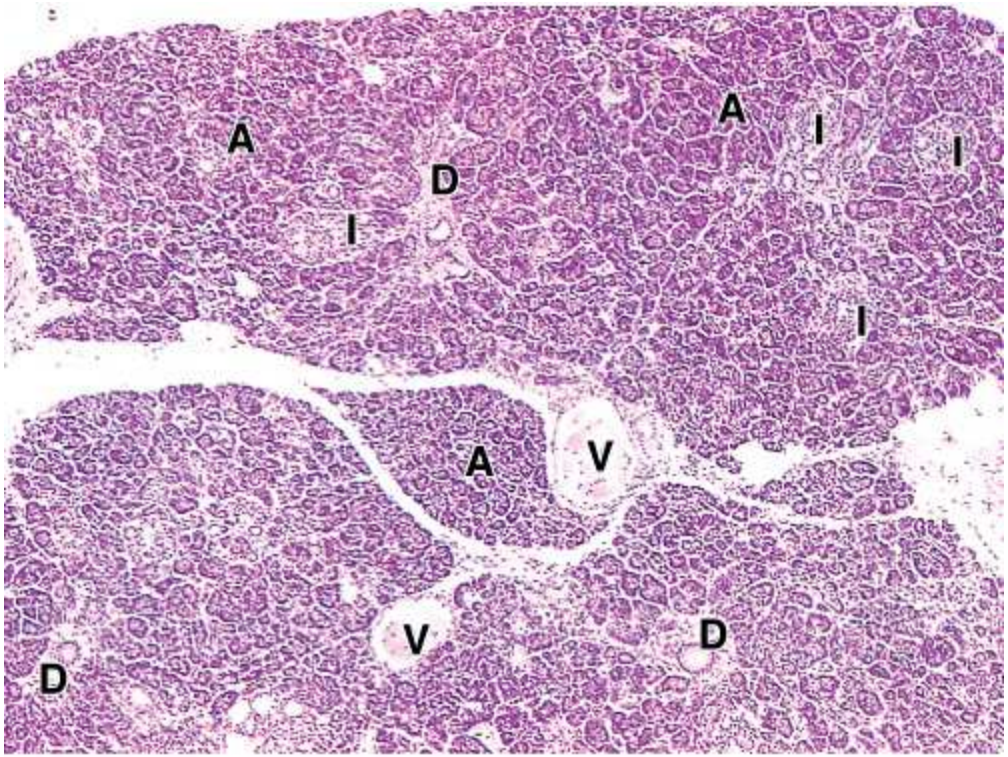


Fig. 16-8 Accessed 02/01/2010

Islets of Langerhans (I) are separated from the acini of the exocrine cells (A) and their ducts (D) by connective tissue. The connective tissue capsule sends septa into the organ to divide it into lobules.

Endocrine pancreas

- Islets of Langerhans are composed of endocrine cells in a rich capillary network.
- Greatest concentration of islets in the tail.
- Autonomic fibers innervate the vessels and endocrine cells.
- Signals spread from cell to cell via gap junctions.
- Signaling also occurs via paracrine mechanism
- Somatostatin-containing δ-cells are neuron-like, creating a network for intra-islet communication.

Endocrine pancreas

- Islet non-β-cells, the α- δ- and pancreatic polypeptide cells (PP-cells), are important components of islet architecture and intercellular communication.

Endocrine pancreas

- α cells
- 20% of islet cells
- Found in periphery of islet
- Produce glucagon
- Somatostatin-2 receptors are also found in α-cells
- Inhibit glucagon secretion
- Secrete acetylcholine, which can act as a paracrine signal to regulate insulin and somatostatin release
- Produce incretin (GLP-1)
- L-cells in gut and brain also produce GLP-1

Glucagon

- Found in electron-dense granules
- Granule exocytosis is calcium-dependent via P/Q-type Ca^{2+}-channels, which may be clustered at designated cell membrane sites
- Production stimulated by hypoglycemia
- Inhibited by hyperglycemia
- Negative regulator of its own secretion
- Glucagon receptors are in the liver.
- Glucagon activates adenyl cyclase, leading to cAMP increase.
- PKA activated, breaking down glycogen
- Reduces plasma triglycerides and stimulates hepatic fatty acid oxidation

Endocrine pancreas

- β cells
- 70% of islet cells
- Found in center of islet
- Produce insulin
- Insulin is secreted into portal system
- 50% degraded in liver
- Remainder exits into peripheral circulation.
- Produce amylin
- Also produce acetylcholine

Insulin

- The principal metabolic function of insulin is to increase the rate of glucose transport into striated muscle cells (including myocardial cells) and to adipocytes.
- The anabolic effects of insulin are attributable to increased synthesis and reduced degradation of glycogen, lipids, and proteins.

Endocrine pancreas

- δ cells
- 10% of islet cells
- Produce somatostatin
- Produced by D cells in the duodenum and intestinal mucosa as well as the hypothalamus
- Calcium dependent release
- Short bioactive half-life of somatostatin
- Inhibitory action via paracrine signaling

Somatostatin

- Release inhibited by vagal action.
- Negatively regulates α- and β-cell function only under conditions of nutrient stimulus.
- Acts as a “buffering hormone”, preventing the over-secretion of insulin or glucagon
- Inhibits gastric acid and pepsinogen secretion
- Inhibits pancreatic and small intestine fluid secretion
- Inhibits gallbladder contraction
- Inhibits both insulin and glucagon release
- Inhibits release of growth hormone in the hypothalamus

Endocrine pancreas

- PP (F) cells
- Produced by PP cells in islets as well as the exocrine pancreas
- Concentrated in the head of the pancreas
- Islets deficient in α-cells
- Vagus nerve as major stimulator
- Released rapidly following a meal
- Remains elevated 4-6 hours
- Pancreatic polypeptide inhibits the release of exocrine pancreatic secretion through feedback on brain receptors to inhibit vagal stimulation of the pancreas.
- Absent in Prader-Willi syndrome

Endocrine pancreas

- D1 cells
- Produce vasoactive intestinal peptide.
- Produced by enteric neurons as well
- Vagal activation
- Induces glycogenolysis
- Stimulates smooth muscle relaxation,
- Stimulates intestinal water and pancreatic bicarbonate secretion
- Secretin agonist

Vasoactive intestinal peptide

- Also serves as immunomodulator balancing T_C and T_H cytokine production
- Is neuroprotective
- Serves as neurotransmitter (non-cholinergic, non-adrenergic)
- Stimulates adenylate cyclase production in the pituitary, affecting glucose homeostasis.

Endocrine pancreas

- G cells
- Produce gastrin
- Produced in the antrum of the stomach
- Rarely found in islets
- Stimulates enterochromaffin-like cells in the pancreas to secrete histamine (and serotonin)
- Stimulates chief cells to produce pepsinogen
- Stimulates parietal cells to produce acid.

Islet architecture

- The localization of the non β-cells predominantly determines the islet architecture
- The vascular supply penetrates the islet center and non-β-cells appear within the core of the islet
- Divides the more central β-cell clusters into units, which have ready access to capillaries.
- “Core-mantle” structure
- Sequential delivery of changes in blood glucose to different cell types based on the direction of blood flow

Islet architecture

- The location of α-cells adjacent to the capillary and in close proximity to the β-cells permits intercellular signaling to create a local, very glucose-sensitive system and immediate adjustment of both insulin and glucagon production for small changes in ambient glucose concentrations.
- Islet architecture is disrupted in Type 1 and Type 2 diabetes, with an increased α-cell population and relocation of non-β-cells to central areas of the islet.
- Non-β-cells are plastic

Islet architecture

- In Type 1 Diabetes, an autoimmune attack destroys the β-cells whereas the non-β-cells remain largely intact.
- The proportion of δ-cells increases
- In Type 2 Diabetes, not only is the β-cell mass affected, but also the α-cell population increases, and extracellular amyloid deposits disrupt the islet architecture
- Somatostatin receptor expression is altered.

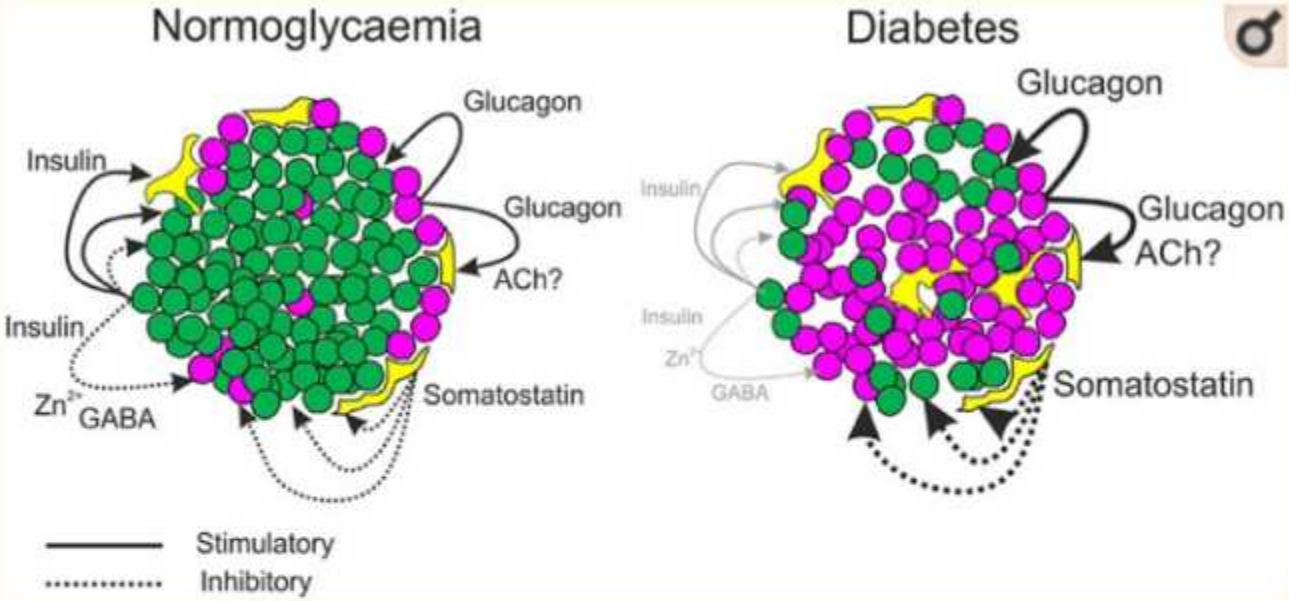


Figure 13.

Diagrammatic representation of intra-islet connections and regulatory signals in health and diabetes. In normoglycemia, cells are closely packed, with non-β-cells situated more peripherally and adjacent to capillaries. Secretion of insulin (green) and glucagon (purple) exert paracrine effects on α-, δ-(yellow), and β-cells. Somatostatin has inhibitory paracrine effects on all cell types (dotted lines). β-Cell products, Zn^{2+} and GABA, may affect α-cell function, and acetylcholine from α-cells may influence somatostatin secretion. In the diabetic islet, architecture is disrupted. There are less β-cells, and α-cells are increased and distributed throughout the islet. The influence of insulin on islet function is reduced but the paracrine effects of glucagon and somatostatin are likely to be increased (heavy solid and dotted lines, respectively).

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4530398/

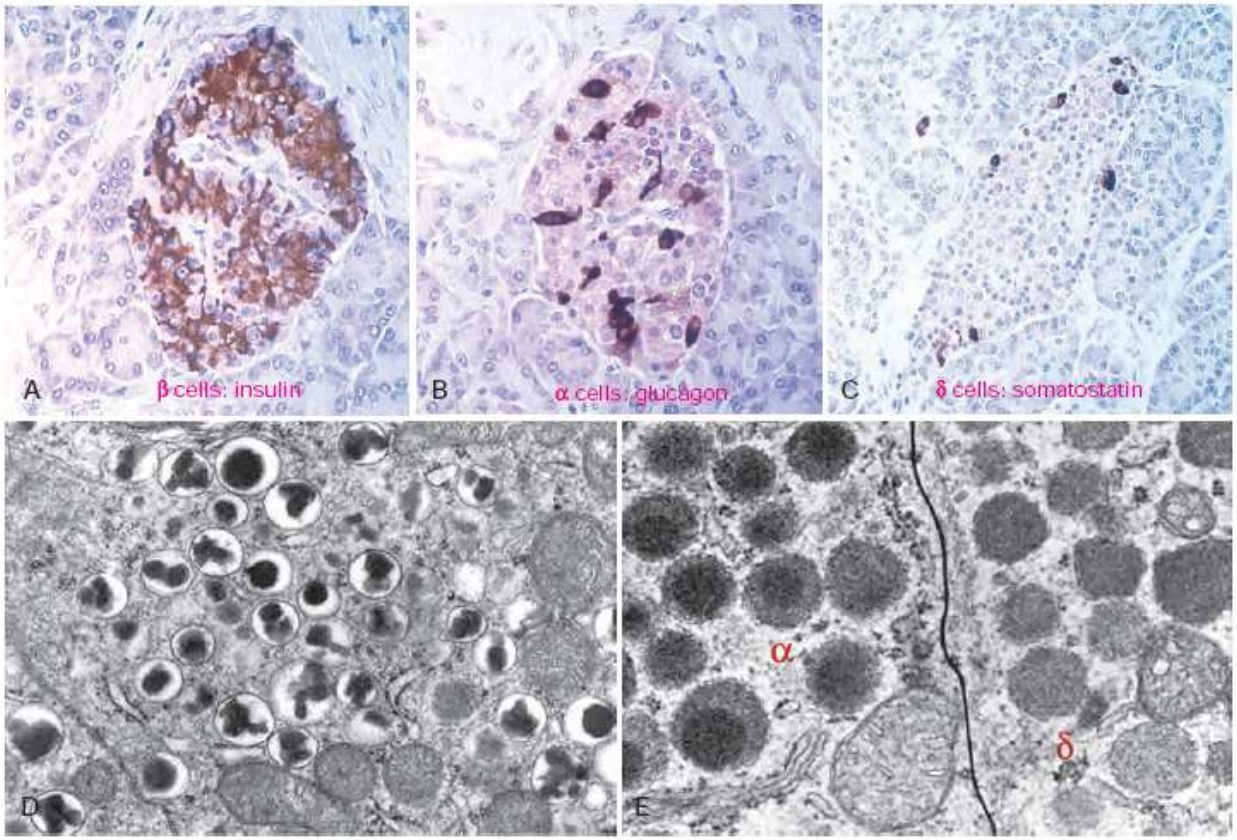
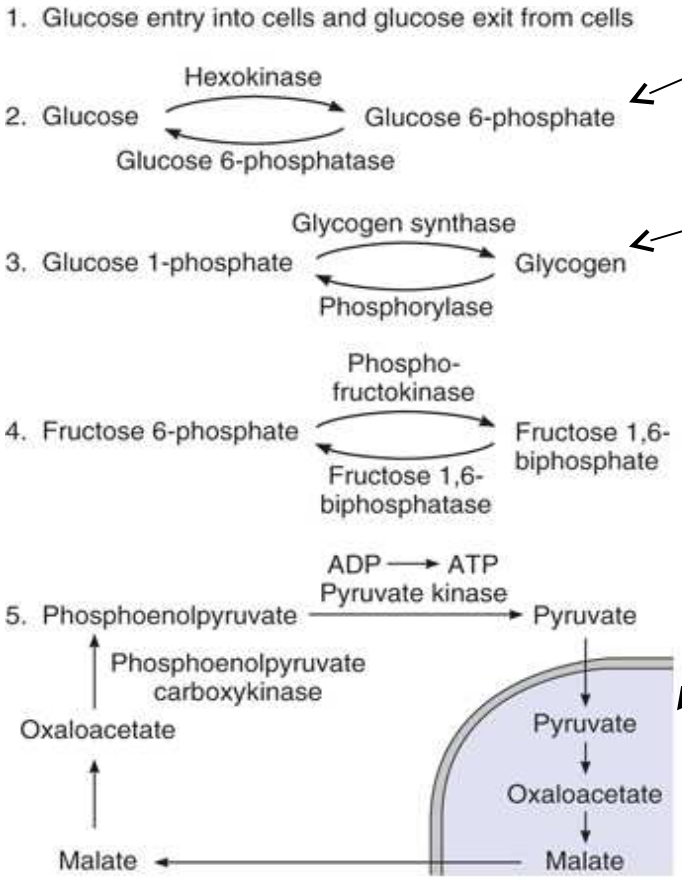


Figure 24-27 Hormone production in pancreatic islet cells. Immunoperoxidase staining shows a dark reaction product for insulin in β cells (**A**), glucagon in α cells (**B**), and somatostatin in δ cells (**C**). **D,** Electron micrograph of a β cell shows the characteristic membrane-bound granules, each containing a dense, often rectangular core and distinct halo. **E,** Portions of an α cell *(left)* and a δ cell *(right)* also show granules, but with closely apportioned membranes. The α-cell granule shows a dense, round center. (Electron micrographs courtesy Dr. Arthur Like, University of Massachusetts Medical School, Worcester, Mass.)

Diabetes mellitus

- Diabetes is a bi-hormonal disease
- Insufficient glucagon secretion at low glucose (when it is needed)
- Excessive release at high glucose (when it is not needed)
- Circadian function impaired

Directional flow



Glucokinase conversion of glucose in the liver is irreversible. Hexokinase, a glucokinase isomer, operates at a lower K_m. (muscle)

Glycogen phosphorylase B is the rate limiting enzyme.

PFK catalysis is the rate limiting step in glucose metabolism

Pyruvate carboxylase is the rate limiting enzyme in gluconeogenesis (in the mitochondrion).

Fig. 1-23 Accessed 07/01/2010

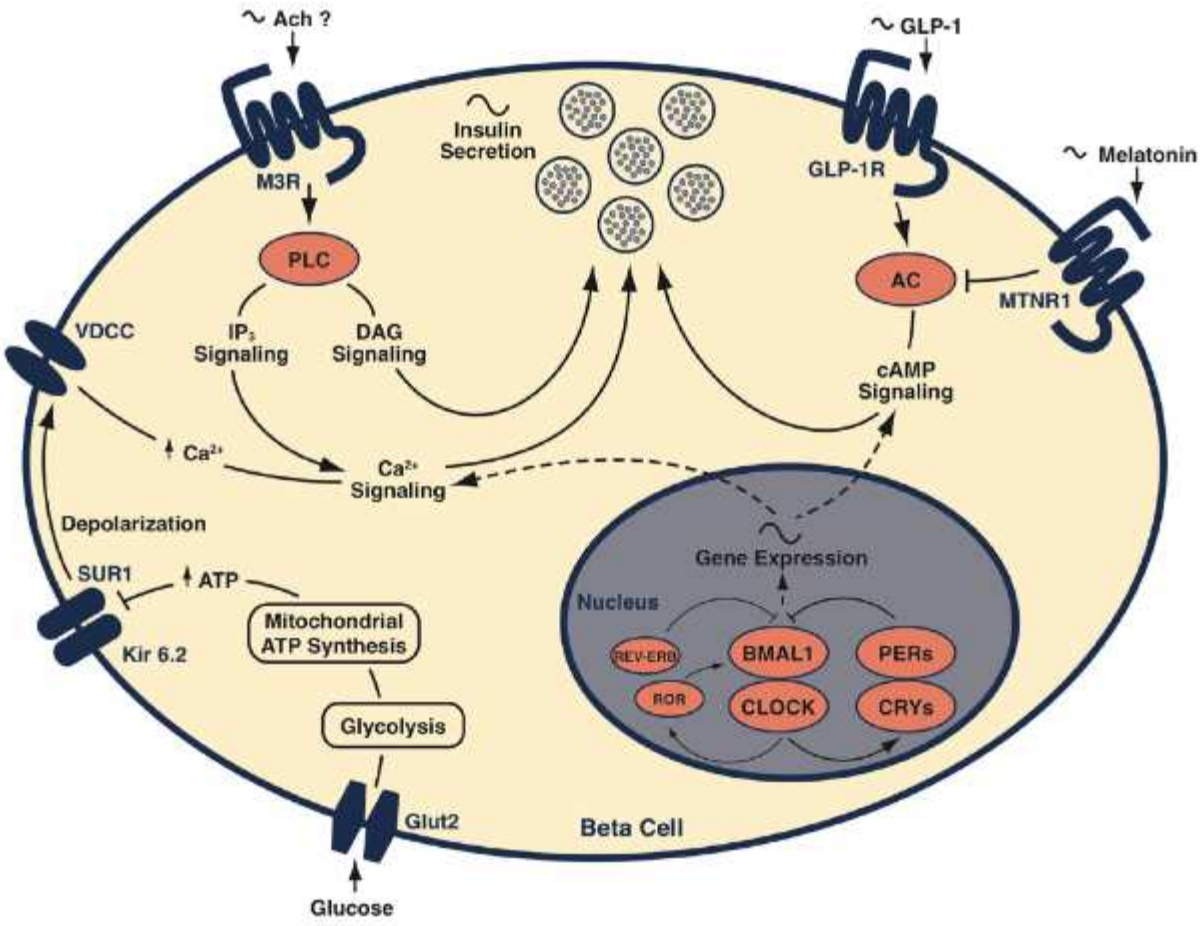


Figure 2. Molecular clock in the beta cell regulates insulin secretion together with circulating systemic factors. The circadian system regulates insulin secretion by driving rhythmic transcription of gene networks involved in glucose-, cAMP-, and Ca^{2+}-stimulated exocytosis. Circulating levels of GLP-1 and melatonin modulate insulin secretion by augmenting or reducing intracellular cAMP levels, respectively. Acetylcholine-stimulated DAG synthesis bypasses clock-controlled signaling pathways to promote insulin secretion, possibly linking brain-derived cholinergic signals to the temporal control of beta cell function.

https://www.researchgate.net/figure/molecular-clock-in-the-beta-cell-regulates-insulin-secretion-together-with-circulating_fig2_305482494

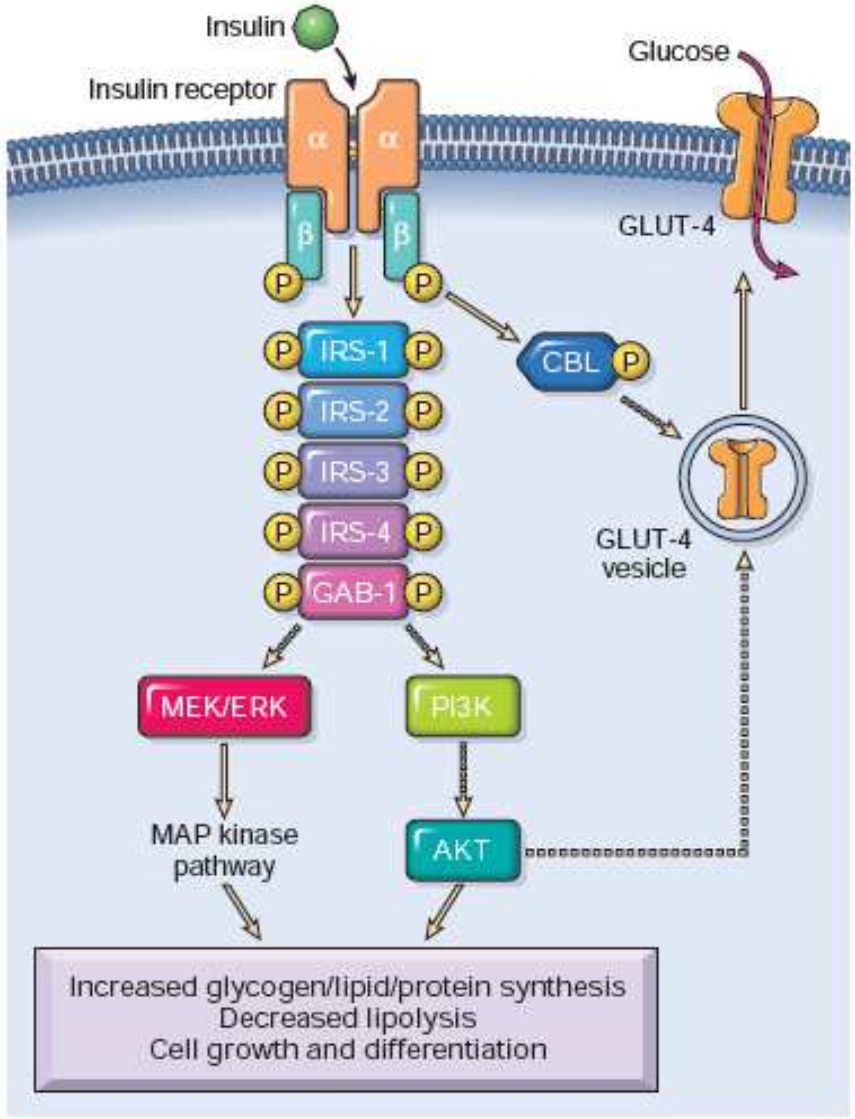


Figure 24-30 Insulin action on a target cell. The metabolic actions of insulin include promoting glycogen synthesis by activating glycogen synthase, and enhancing protein synthesis and lipogenesis while inhibiting lipolysis (see text). Dashed arrows represent intermediate proteins and binding partners that are not shown in this overview diagram.

Glucose homeostasis

- Glucose rise leads to increased uptake of glucose into pancreatic β-cells (insulin independent Glut2 transporter).
- There is an ATP-sensitive K^+ channel on the β-cells comprised of an inward rectifying K^+ channel and the sulfonylurea receptor.
- As glucose is metabolized and ATP generated, the channel is inhibited and the membrane depolarizes.
- There is an influx of Ca^{2+} through a voltage dependent Ca^{2+} channel.
- Rising intracellular Ca^{2+} levels stimulate insulin release from stores in β-cell granules.

Glucose homeostasis

- Two incretins have been identified:
- Glucose-dependent insulinotropic polypeptide (GIP)
- Secreted by enteroendocrine “K cells” in the proximal small bowel
- Glucagon-like peptide-1 (GLP-1)
- Secreted by “L cells” in the distal ileum and colon.
- The elevation in GIP and GLP-1 levels following oral food intake is known as the “incretin effect.”

Glucose homeostasis

- In addition to increased insulin secretion from β cells, these hormones also reduce glucagon secretion and delay gastric emptying, which promotes satiety.
- Once released, circulating GIP and GLP-1 are degraded in circulation by dipeptidyl peptidase (DPPs), especially DPP-4.

Glucose set points

- Glucose ~55 mg/dl promotes cortisol secretion.
- Glucose ~70 mg/dl promotes glucagon secretion from islet cells.
- Epinephrine and growth hormone secretion also increase.
- Glucose ~85 mg/dl inhibits insulin secretion from the β-cell.
- GPK is rate-limiting step in β-cell.
- Regulation of glucose production by liver is predominant determinant of glucose level.

Diagnosis of diabetes

Diagnosis	A1C (percent)	Fasting plasma glucose (FPG)[a]	Oral glucose tolerance test (OGTT)[ab]	Random plasma glucose test (RPG)[a]
Normal	below 5.7	99 or below	139 or below	
Prediabetes	5.7 to 6.4	100 to 125	140 to 199	
Diabetes	6.5 or above	126 or above	200 or above	200 or above

[a]Glucose values are in milligrams per deciliter, or mg/dL.

[b]At 2 hours after drinking 75 grams of glucose. To diagnose gestational diabetes, health care professionals give more glucose to drink and use different numbers as cutoffs.

https://www.niddk.nih.gov/health-information/diabetes/overview/tests-diagnosis

Table 24-6 Classification of Diabetes Mellitus

Type 1 diabetes (β-cell destruction, usually leading to absolute insulin deficiency)
Immune-mediated Idiopathic
Type 2 diabetes (combination of insulin resistance and β-cell dysfunction)
Genetic defects of β-cell function
Maturity-onset diabetes of the young (MODY), caused by mutations in: Hepatocyte nuclear factor 4α (*HNF4A*), MODY1 Glucokinase (*GCK*), MODY2 Hepatocyte nuclear factor 1α (*HNF1A*), MODY3 Pancreatic and duodenal homeobox 1 (*PDX1*), MODY4 Hepatocyte nuclear factor 1β (*HNF1B*), MODY5 Neurogenic differentiation factor 1 (*NEUROD1*), MODY6 Neonatal diabetes (activating mutations in *KCNJ11* and *ABCC8*, encoding Kir6.2 and SUR1, respectively) Maternally inherited diabetes and deafness (MIDD) due to mitochondrial DNA mutations (m.3243A→G) Defects in proinsulin conversion Insulin gene mutations
Genetic defects in insulin action
Type A insulin resistance Lipoatrophic diabetes
Exocrine pancreatic defects
Chronic pancreatitis Pancreatectomy/trauma Neoplasia Cystic fibrosis Hemochromatosis Fibrocalculous pancreatopathy
Endocrinopathies
Acromegaly Cushing syndrome Hyperthyroidism Pheochromocytoma Glucagonoma
Infections
Cytomegalovirus Coxsackie B virus Congenital rubella
Drugs
Glucocorticoids Thyroid hormone Interferon-α Protease inhibitors β-adrenergic agonists Thiazides Nicotinic acid Phenytoin (Dilantin) Vacor
Genetic syndromes associated with diabetes
Down syndrome Klinefelter syndrome Turner syndrome Prader-Willi syndrome
Gestational diabetes mellitus

American Diabetes Association: Position statement from the American Diabetes Association on the diagnosis and classification of diabetes mellitus. Diabetes Care 31 (Suppl. 1): S55-S60, 2008.

Diabetes mellitus

- Polyuria, polydipsia, weight loss, fatigue
- 10%, Type 1
- 90%, Type 2
- Associated with obesity
- Peripheral resistance to insulin
- Inadequate secretory response of β-cells
- Mature onset diabetes of the young (MODY)
- Neonatal diabetes mellitus

Table 24-7 Type 1 Versus Type 2 Diabetes Mellitus

Type 1 Diabetes Mellitus	Type 2 Diabetes Mellitus
Clinical	
Onset: usually childhood and adolescence	Onset: usually adult; increasing incidence in childhood and adolescence
Normal weight or weight loss preceding diagnosis	Vast majority are obese (80%)
Progressive decrease in insulin levels	Increased blood insulin (early); normal or moderate decrease in insulin (late)
Circulating islet autoantibodies (anti-insulin, anti-GAD, anti-ICA512)	No islet autoantibodies
Diabetic ketoacidosis in absence of insulin therapy	Nonketotic hyperosmolar coma more common
Genetics	
Major linkage to MHC class II genes; also linked to polymorphisms in *CTLA4* and *PTPN22*, and insulin gene VNTRs	No HLA linkage; linkage to candidate diabetogenic and obesity-related genes (*TCF7L2, PPARG, FTO*, etc.)
Pathogenesis	
Dysfunction in T cell selection and regulation leading to breakdown in self-tolerance to islet autoantigens	Insulin resistance in peripheral tissues, failure of compensation by β-cells
	Multiple obesity-associated factors (circulating nonesterified fatty acids, inflammatory mediators, adipocytokines) linked to pathogenesis of insulin resistance
Pathology	
Insulitis (inflammatory infiltrate of T cells and macrophages) β-cell depletion, islet atrophy	No insulitis; amyloid deposition in islets Mild β-cell depletion

HLA, Human leukocyte antigen; MHC, major histocompatibility complex; VNTRs, variable number of tandem repeats.

Type1 diabetes mellitus

- The fundamental immune abnormality in type 1 diabetes is a failure of self-tolerance in T cells specific for islet antigens.
- The initial activation of T-cells is thought to occur in the peripancreatic lymph nodes.
- The activated T-cells then traffic to the pancreas
- T_{H1} and CD8+ cytotoxic lymphocytes involved in β-cell damage.
- Molecular mimicry of virus as possible trigger (Coxsackie B)

Type1 diabetes mellitus

- The disease has strong HLA associations
- 90-95% of Europeans with this disease have either an HLA-DR3 or HLA-DR4 haplotype
- Normal population distribution is 40%
- 40% to 50% of patients are combined DR3/DR4 heterozygotes
- Normal population distribution is 5%
- One of the highest inherited risks is the association of D3 or D4 with DQ8
- Alterations are near peptide pockets and may affect antigen presentation.

Type1 diabetes mellitus

- Autoimmune markers include:
- Islet cell autoantibodies
- Autoantibodies to insulin
- Autoantibodies to GAD (GAD65)
- Autoantibodies to the tyrosine phosphatases IA-2 and IA-2β
- Autoantibodies to zinc transporter 8 (ZnT8).
- 70% of those who developed more than two autoantibodies, developed type 1 diabetes within 10 years, and 84% within 15 years

Type1 diabetes mellitus

- Altered T-cell selection and regulation
- Mutated CTLA4 gene at 2q33.2
- Inhibitory receptor acting as a major negative regulator of T-cell responses
- Mutated PTPN22 gene at 1p13.2
- Involved in signal transduction that helps control the activity of T cells.
- VNTR polymorphism 5’ to insulin gene may affect insulin transcription.

Type 2 diabetes mellitus

- 80% concordance in monozygotic twins
- Up to 40% if both parents have disease
- >80% of patients are obese
- Prevalent among Native Americans and those of African ancestry.
- Haplotypes that protect against diabetes mellitus:
- DQA1*0102, DQB1*0602
- Found in 20% of the normal population but are rarely found in patients with diabetes mellitus.

Type 2 diabetes mellitus

- Decreased response of peripheral tissues, especially skeletal muscle, adipose tissue, and liver, to insulin (insulin resistance)
- Predates hyperglycemia
- Accompanied by increase in β-cell mass
- Inadequate insulin secretion in the face of insulin resistance and hyperglycemia (β-cell dysfunction)

Insulin resistance

- (1) Failure of glucose uptake and glycogen synthesis in skeletal muscle following a meal.
- Increased translocation of GLUT-4 to surface of skeletal muscle noted with exercise
- (2) Failure to inhibit lipoprotein lipase in adipose tissue, leading to excess circulating free fatty acids (FFAs)
- Predilection for central adipose sites
- FFAs are proinflammatory

Insulin resistance

- (3) FFAs compete with glucose for substrate oxidation, leading to feedback inhibition of glycolytic enzymes
- Failure to inhibit endogenous glucose production (gluconeogenesis) in the liver
- Peroxisome proliferator-activated receptor gamma (PPARγ) of adipocyte involved in cytokine secretion and regulation of levels of free fatty acids.
- Defect increases risk 25%
- Common in those of European ancestry.
- Leptin and adiponectin increase sensitivity to insulin via cAMP activation of MAPK pathway
- Reduce fatty acid oxidation

β-cell dysfunction

- Excess free fatty acids that compromise β cell function and attenuate insulin release (“lipotoxicity”)
- The impact of chronic hyperglycemia (“glucotoxicity”)
- An abnormal “incretin effect,” leading to reduced secretion of GIP and GLP-1,
- Amyloid deposition within islets.

Pharmacologic interventions

- Diabetes mellitus type 2
- Thiazolidinediones (glitazones) reduce insulin resistance by modulating Peroxisome proliferator active receptor-gamma (PPARγ) nuclear receptor as agonist ligands
- Promotes secretion of anti-hyperglycemic adipokines.
- Inhibits JNK enzyme, associated with insulin resistance.
- Associated with weight gain
- Metformin targets MAPK pathway
- Weight neutral

Pharmacologic interventions

- GLP1 agonist
- Effective in inducing and sustaining weight loss
- 5-10% weight loss independent of glycemic control
- Liraglutide is a weekly subcutaneous injection
- Not for use in MEN2
- Semaglutide as daily subcutaneous injection more effective than pill
- Diminishes gastric emptying
- Neuroprotective
- Diminishes incidence of adverse cardiovascular events

Pharmacologic interventions

- SGLT2 (flozins)
- Works in proximal tubule
- Block Na^+-glucose transport protein as well as Na^+-HCO_3^- transport.
- Promotes osmotic diuresis (rapid weight loss)
- Diminishes hyperfiltration
- International guidelines promote use with ACE inhibitors or Angiotensin Receptor Blockers for the control of hyperglycemia in patients with chronic kidney disease.
- Dafagliflozin if renal disease, established coronary artery disease, diminished ejection fraction
- Canagliflozin if preserved ejection fraction as well

Pharmacologic interventions

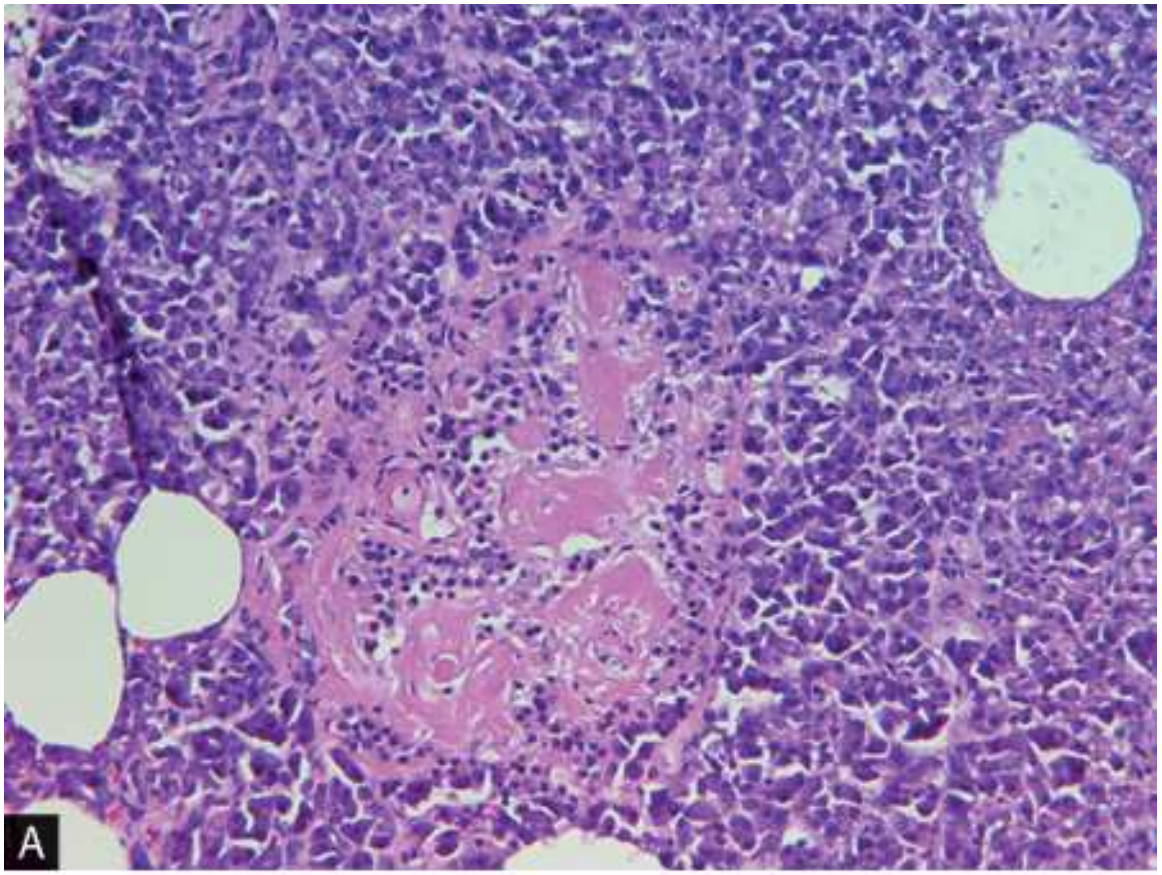
- PPARy and SGLT2 diminish LDL clearance
- GLP1 and SGLT2 associated with improved HbA_{1c} and blood pressure control
- SGLT-2 inhibitor slows progression in chronic kidney disease
- Improved gout outcomes

Pharmacologic interventions

- Bempedoic acid is an ATP-citrate lysase inhibitor
- Catalyzes the conversion of citrate and coenzyme A (CoA) to acetyl-CoA and oxaloacetate, with the simultaneous hydrolysis of ATP to ADP and phosphate
- Reduces LDL cholesterol and high-sensitivity C-reactive protein and risk of cardiovascular events.
- Patients without diabetes had no increase in new-onset diabetes or worsening HbA_{1c} with bempedoic acid.

Histopathology of pancreas

- Type 1
- Diminished numbers of islets
- T-cell infiltration of islets
- Type 2
- Diminished β-cell mass
- Amyloid deposition in and around capillaries and between cells
- Neonates born to diabetic mothers
- Islet hyperplasia



The single islet in the center is obliterated by acellular eosinophilic material that has apple-green birefringence on Congo Red stain. This is amyloid (amylin).

Source: Kemp WL, Burns DK, Brown TG: *Pathology: The Big Picture*: www.accessmedicine.com

Figure 18-11A. Accessed October 25, 2015

Histopathology of arteries

- Accelerated atherosclerosis in aorta as well as large and medium sized arteries.
- Myocardial infarction is most common cause of death
- Gangrene of lower extremities as a result of arteriosclerotic disease
- Renal hyaline arteriosclerosis
- Diabetic capillaries are more leaky than normal to plasma proteins.
- The microangiopathy underlies the development of diabetic nephropathy, retinopathy, and some forms of neuropathy.

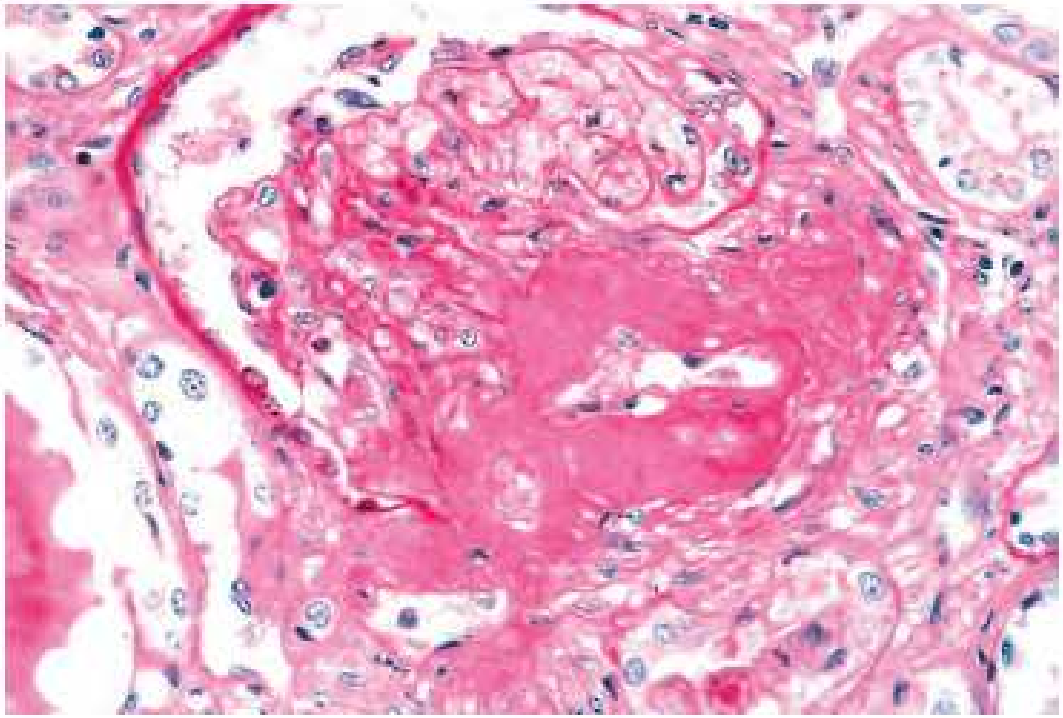


Figure 24-36 Severe renal hyaline arteriolosclerosis. Note a markedly thickened, tortuous afferent arteriole. The amorphous nature of the thickened vascular wall is evident. (PAS stain). (Courtesy M.A. Venkatachalam, MD, Department of Pathology, University of Texas Health Science Center at San Antonio, Texas.)

Nephropathy

- Asymptomatic until renal failure presents
- Most common cause of end stage renal disease
- Microalbuminuria presents 10-15 years after onset of diabetes mellitus; progresses in 80% over the ensuing 10-15 years
- End stage renal disease develops in 50% of type I diabetes mellitus patients with overt nephropathy within 10 years (75%, 20 years); for type II, 20% within 20 years

Histopathology of kidneys

- Renal failure is second only to myocardial infarction as a cause of death from this disease.
- Three lesions are encountered:
- (1) glomerular lesions
- (2) renal vascular lesions, principally arteriolosclerosis
- (3) pyelonephritis, including necrotizing papillitis.

Histopathology of kidneys

- The most important glomerular lesions are:
- (1) Capillary basement membrane thickening
- Thickening begins as early as 2 years after the onset of type 1 diabetes and by 5 years amounts to about a 30% increase.
- The thickening continues progressively and usually concurrently with mesangial widening.
- Simultaneously, there is thickening of the tubular basement membranes

Histopathology of kidneys

- (2) Diffuse mesangial sclerosis
- The mesangial increase is typically associated with the overall thickening of the GBM.
- The matrix depositions are PAS-positive
- The expansion of mesangial areas can extend to nodular configurations.
- The progressive expansion of the mesangium has been shown to correlate well with deteriorating function.
- Mesangial cell proliferation is not marked.

Histopathology of kidneys

- (3) Nodular glomerulosclerosis.
- Intercapillary glomerulosclerosis (Kimmelstiel-Wilson disease).
- The glomerular lesions take the form of ovoid or spherical, often laminated, nodules of matrix situated in the periphery of the glomerulus.
- The nodules are PAS-positive.
- They lie within the mesangial core of the glomerular lobules and can be surrounded by patent or dilated peripheral capillary loops.
- Capillary microaneurysms also present.

Histopathology of kidneys

- These nodular lesions are frequently accompanied by prominent accumulations of hyaline material in capillary loops ("fibrin caps") or adherent to Bowman capsules ("capsular drops").
- Both afferent and efferent glomerular hilar arterioles show hyalinosis.
- Ischemic damage.
- May lead to atrophy and tubulointerstitial fibrosis.
- Pyelonephritis and papillary necrosis may result.
- 15-35% patients with long-term diabetes.

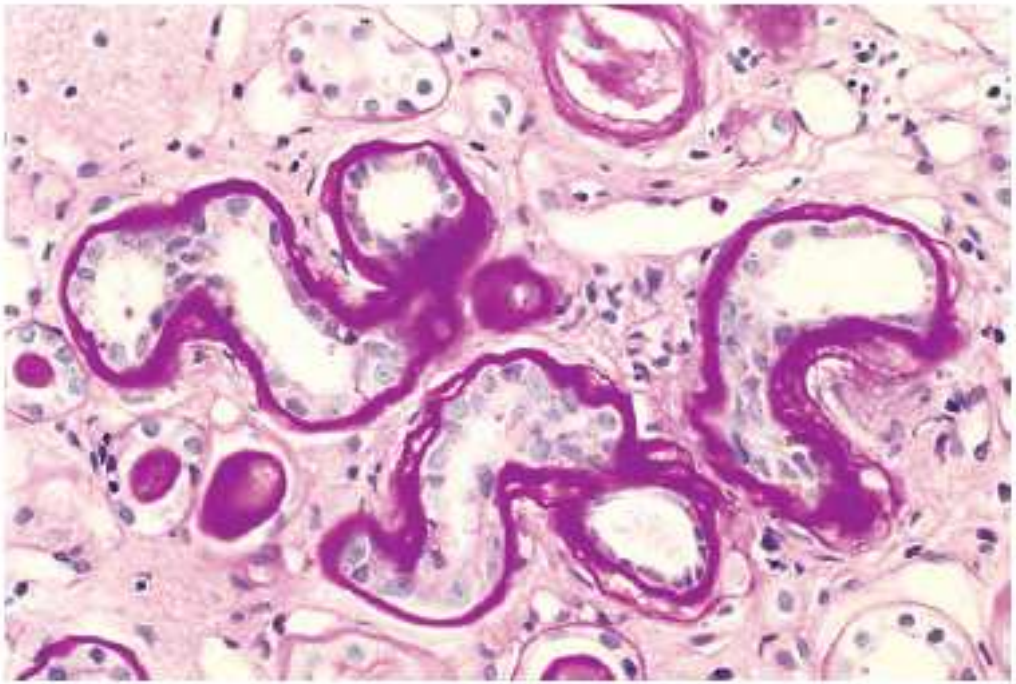


Figure 24-38 Renal cortex showing thickening of tubular basement membranes in a diabetic patient (PAS stain).

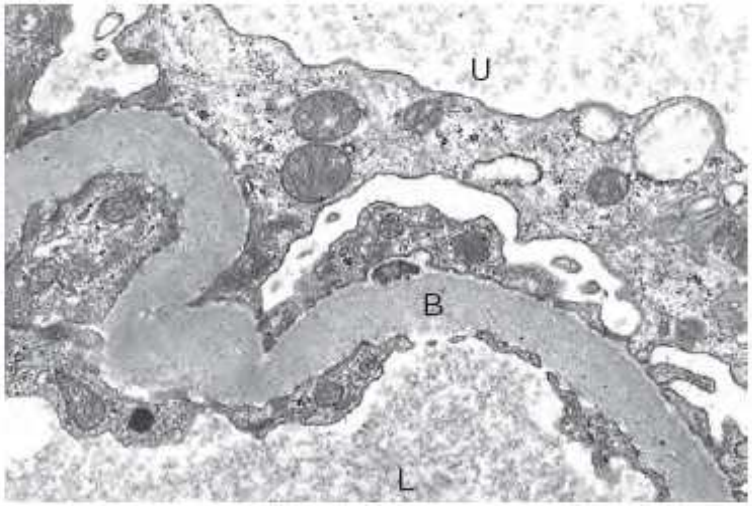


Figure 24-37 Electron micrograph of a renal glomerulus showing markedly thickened glomerular basement membrane (B) in a diabetic. L, glomerular capillary lumen; U, urinary space. (Courtesy Dr. Michael Kashgarian, Department of Pathology, Yale University School of Medicine, New Haven, Conn.)

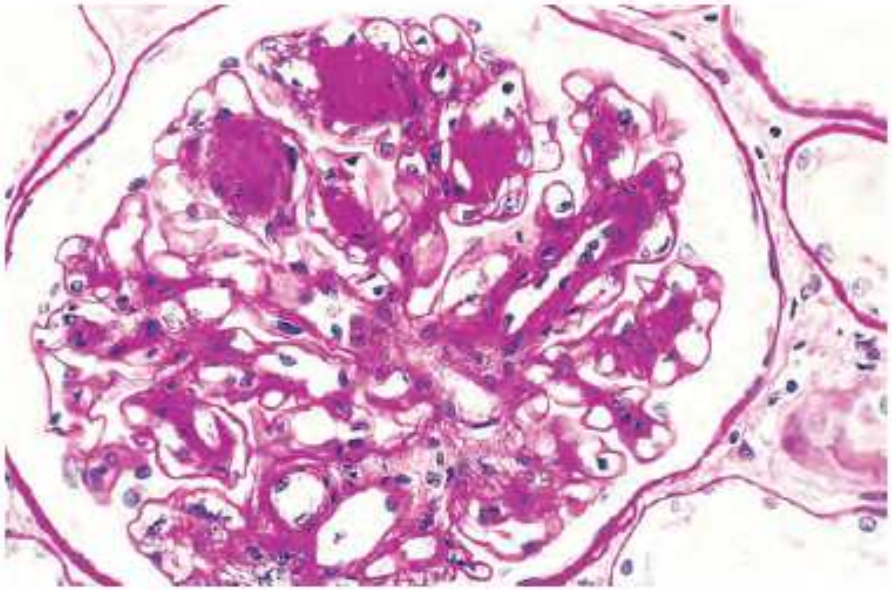


Figure 24-39 Diffuse and nodular diabetic glomerulosclerosis (PAS stain). Note the diffuse increase in mesangial matrix and characteristic acellular PAS-positive nodules.

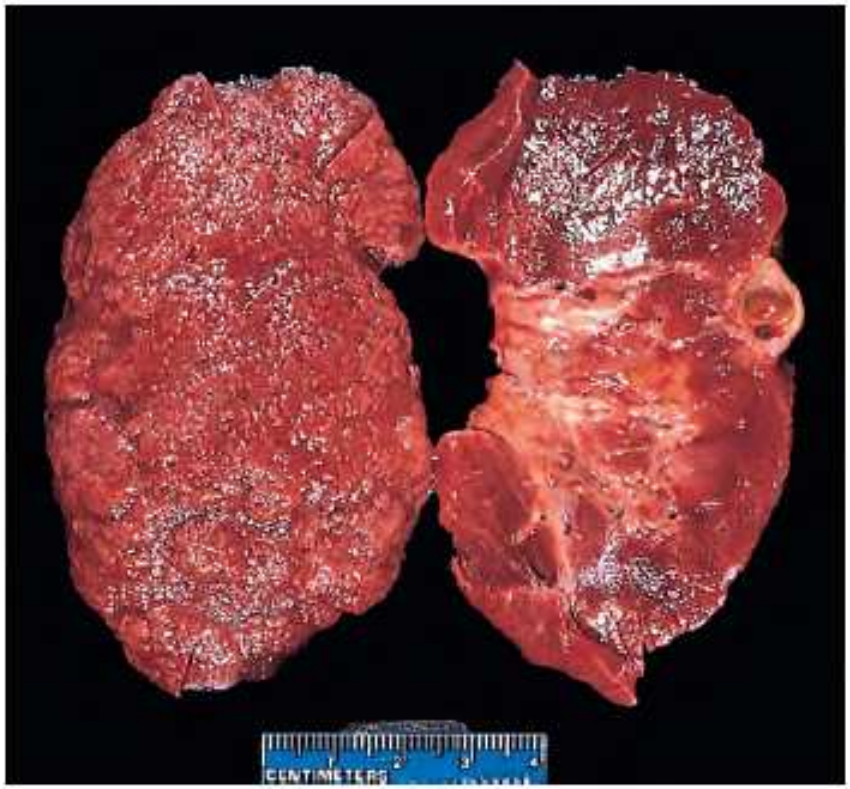


Figure 24-40 Nephrosclerosis in a patient with long-standing diabetes. The kidney has been bisected to demonstrate both diffuse granular transformation of the surface *(left)* and marked thinning of the cortical tissue *(right)*. Additional features include some irregular depressions, the result of pyelonephritis, and an incidental cortical cyst *(far right)*.

Neuropathy

- Up to 50% of diabetics overall have peripheral neuropathy clinically, and up to 80% of those who have had the disease for more than 15 years
- Peripheral nerve lesions present as paresthesias or burning pain in a stocking-glove distribution.
- Worse at night.
- If cranial neuropathy (rare), usually CN III or VI
- Transient

Neuropathy

- Mononeuropathy.
- Median nerve most common site (6%).
- Ulnar (2%), femoral, and peroneal nerves affected as well.
- Loss of ankle reflexes.
- Loss of vibratory, pain, temperature, pressure sensation

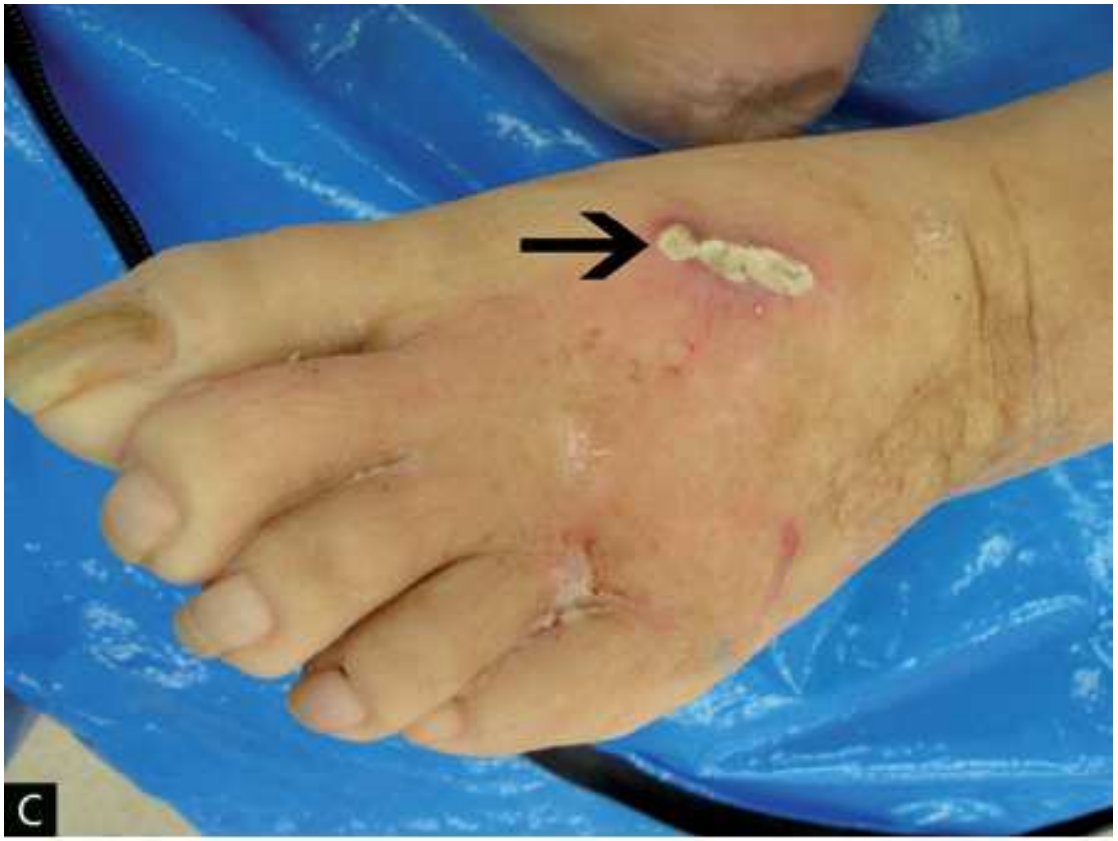
Neuropathy

- Lifetime risk of developing a foot ulcer is about 15%
- 90% if diabetics with foot ulcers have neuropathy
- Remainder, peripheral vascular disease involving tibio-peroneal vessels
- Occur at pressure points (plantar surfaces, calluses)
- Arterial ulcers occur on toes or shins
- Venous ulcers occur above the malleoli
- Limb-threatening if ulcerate to deep tissues
- OR have extensive purulent drainage or cellulitis extending more than 2cm from the ulcer
- OR lymphangitis

Neuropathy

- Osteomyelitis develops in 15% (biopsy to demonstrate as well as to culture).
- Polymicrobial; anerobes common

Neuropathy



Source: Kemp WL, Burns DK, Brown TG: *Pathology: The Big Picture*: www.accessmedicine.com

Due to loss of sensation secondary to peripheral neuropathy and poor circulation due to vascular damage, diabetics are prone to develop non-healing ulcers (arrow) of the extremities.

Figure 18-11C. Accessed October 25, 2015

Myopathy

- Diabetic amyotrophy.
- Pain, severe asymmetric muscle weakness, and wasting of the iliopsoas and quadriceps muscles noted (late).
- Tarsometatarsal Charcot joints in 10% of patients with neuropathy
- 15% lifetime risk of amputation

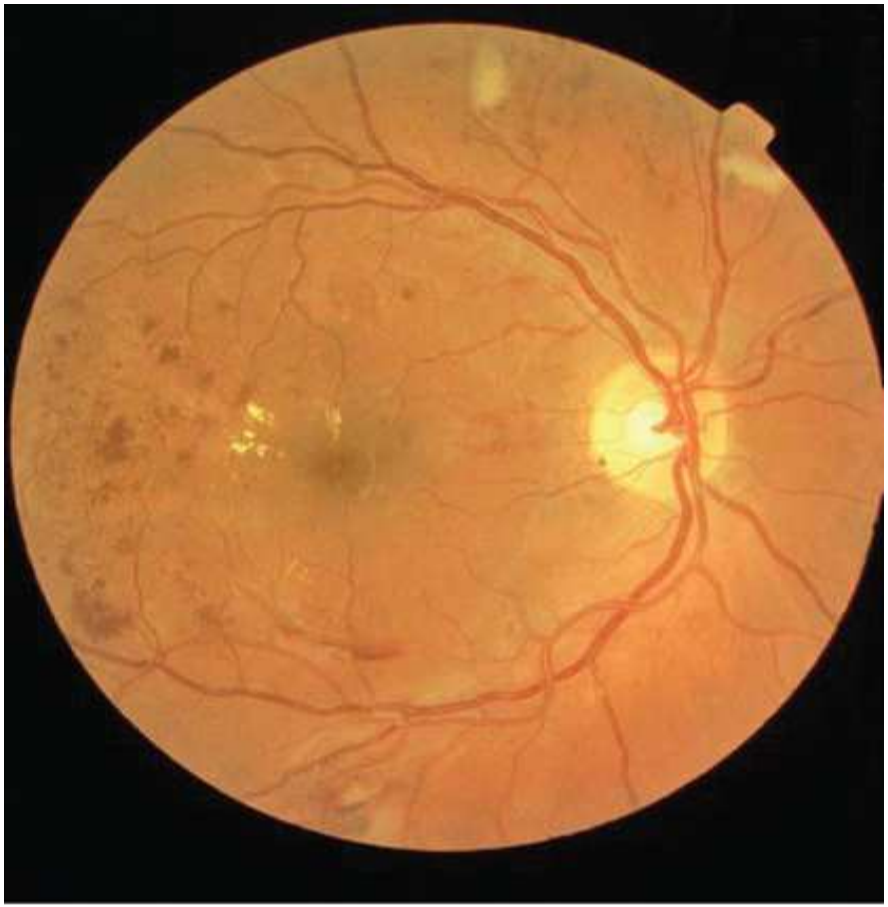
Neuropathy

- Autonomic disturbances in 28-45%
- Orthostatic hypotension (>30 mmHg fall with postural change)
- Gustatory sweating
- Diarrhea
- Urinary incontinence
- Detrusor muscle hypercontractility with concomitant diminished sensation of bladder filling
- Gastroparesis (delayed gastric emptying)
- Erectile dysfunction
- Constipation in 20% of type 2 patients

Histopathology of other organs

- Diabetes-induced hyperglycemia leads to acquired opacification of the lens (cataract).
- Long-standing diabetes is also associated with increased intraocular pressure (glaucoma), and resulting damageto the optic nerve.
- The retinal vasculopathy of diabetes mellitus can be classified into background (preproliferative) diabetic retinopathy and proliferative diabetic retinopathy.

Non-proliferative retinopathy



Source: Riordan-Eva P, Cunningham E: *Vaughan & Asbury's General Ophthalmology*, 18th Edition: http://www.accesmedicine.com

Figure 10-6. Accessed October 25, 2015

Vision symptoms are caused by macular edema or macular ischemia. However, patients may not have vision loss even with advanced retinopathy. The first signs of nonproliferative retinopathy are: capillary microaneurysms; dot and blot retinal hemorrhages; hard exudates; cotton-wool spots (soft exudates)

Proliferative retinopathy

Figure 39-17. Accessed October 25, 2015

Hard exudates are discrete, yellow particles within the retina. When present, they suggest chronic edema. Here they are at the macula. Cotton-wool spots are areas of microinfarction of the retinal nerve fiber layer that lead to retinal opacification; they are fuzzy-edged and white and obscure underlying vessels. Neovascular vessels emanate from the optic disc. Round spots in the periphery represent recently applied panretinal photocoagulation.

Table 25.6 Contrasting features of type 1 and type 2 diabetes mellitus.

	FEATURE	TYPE 1 DM	TYPE 2 DM
1.	*Frequency*	10-20%	80-90%
2.	*Age at onset*	Early (below 35 years)	Late (after 40 years)
3.	*Type of onset*	Abrupt and severe	Gradual and insidious
4.	*Weight*	Normal	Obese/non-obese
5.	*HLA*	Linked to HLA DR3, HLA DR4, HLA DQ	No HLA association
6.	*Family history*	< 20%	About 60%
7.	*Genetic locus*	Unknown	Chromosome 6
8.	*Diabetes in identical twins*	50% concordance	80% concordance
9.	*Pathogenesis*	Autoimmune destruction of β-cells	Insulin resistance, impaired insulin secretion
10.	*Islet cell antibodies*	Yes	No
11.	*Blood insulin level*	Decreased insulin	Normal or increased insulin
12.	*Islet cell changes*	Insulitis, β-cell depletion	No insulitis, later fibrosis of islets
13.	*Amyloidosis*	Infrequent	Common in chronic cases
14.	*Clinical management*	Insulin and diet	Diet, exercise, oral drugs, insulin
15.	*Acute complications*	Ketoacidosis	Hyperosmolar coma

Mohan, H, Textbook of Pathology, 7th ed., Health Science Publishers. New Delhi. 2015.

Obesity

- Don’t blame it on leptin.
- Produced in adipocytes
- Signals hypothalamus that adipose stores are sufficient.
- Interacts with POMC (anorexigenic) and arginine related protein (orexigenic as it blocks α-MSH) as well as the abundant Neuropeptide Y (orexigenic).
- Normal BMI >18-25 kg/m^2
- Overweight children if weight >85^{th} percentile; obesity if >95^{th} percentile

Obesity

- Definition of obesity differs among those of Asian ancestry (>25), European ancestry (>30), and African ancestry (>34).
- Waist circumference greater discriminator in Hawaiian-Phillipine Islander populations (>88cm in women, 90cm in men)
- An elevated BMI is associated with a health risk comparable to tobacco use
- Obesity is associated with 2-4 years loss of life expectancy
- A BMI>40, a loss of 8-10 years

Obesity

- Any diet to which the patient adheres is more effective than no intervention
- Exercise diminishes resistance to endogenous insulin
- However, not associated with weight loss

Metabolic syndrome

- Defined by three of the following five:
- Abdominal obesity
- Elevated fasting triglycerides (>150mg/dl)
- HDL depressed (<40mg/dl in men, 50mg/dl in women)
- Hypertensive (>130/85 mmHg)
- Hyperglycemic (random fasting glucose >100mg/dl)

Metabolic syndrome

- Metabolic syndrome doubles risk for cardiovascular events
- Behavioral modification effective in children
- High levels of antioxidant enzyme levels associated with risk reduction independent of Coenzyme Q and vitamin E levels

MODY

- Maturity onset diabetes of the young
- Early-onset diabetes in adolescence or young adulthood (typically age <35 years)
- Absence of autoantibodies
- Measurable C-peptide in the presence of hyperglycemia
- Low insulin dose for control
- No spontaneous ketoacidosis
- 10%, mutations in transcription factors: HNF-4α, HNF-1β, insulin promoter factor (IPF)-1, and NeuroD1.

MODY

- 60%, Hepatocyte nuclear factor (HNF)-1α gene mutation at 12p24.31
- Late adolescence
- Progressive β-cell dysfunction with increased insulin sensitivity and glucosuria
- 15%, Glucokinase gene mutation at 7p13
- Converts glucose to glucose-6-phosphate, the metabolism of which, in turn, stimulates insulin secretion by the β-cell.
- Mild fasting hyperglycemia at birth
- Generally asymptomatic

Pathogenesis

- Glucokinase irreversibly catalyzes the phosphorylation of glucose to Glucose-6-Phosphate
- The first and rate limiting step in glucose metabolism.
- High K_m.
- Glucokinase is found only in the liver.
- G6P undergoes glycolysis and is transformed into Fructose-1,6 biphosphate.
- This is the rate limiting step in glycolysis.
- Cortisol stimulates reaction.
- Sensitive to AMP levels.

Pathogenesis

- Insulin stimulates Fructose 1,6 Biphosphate conversion into DHAP
- Drives glycolysis by regenerating ATP and NADH lost in the process to this point
- Drives glycolysis into pyruvate
- Driven by glucagon.

Pathogenesis

- Hexokinase is operative at a lower K_m than is glucokinase in the liver.
- Hexokinase is found in other organs.
- The reaction phosphorylating glucose is reversible.
- Glucose-6-phosphatase (found also in the kidney) permits catabolism of Glucose-6-Phosphate.
- Slower metabolism and ATP generation limit response of ATP-sensitive K^+ channel in β-cell.
- Hyperglycemia results.

Table 1: Common forms of MODY		
Classification	**Gene mutation**	**Comments**
MODY 1	HNF 4 alpha	Responsive to sulphonylureas. May later need insulin
MODY 2	Glucokinase	Often asymtomatic. Low risk of complications. May not require treatment
MODY 3	HNF 1 alpha	Most common form of MODY in the UK. Resporesive to sulphonylureas
MODY 5	HNF 1 beta	Associated with renal cysts, uterine abnormalities, gout. Tends to develop later than other forms of MODY

Neonatal diabetes

- Hyperglycemia at birth
- Transient disease is related to a defect on ZAC/HYAMI imprinting at 6q24
- Permanent neonatal diabetes is most commonly a defect in the KCNJ11 gene at 11p15.1 encoding a subunit of the β-cell K_{ATP} channel.
- The INS (insulin) gene is at 11p15.5
- Hyperglycemia persists beyond 6 months
- May be associated with developmental delay and epilepsy (DEND syndrome)
- Can be well managed with sulfonylureas.

Insulin resistance syndromes

- Hypertriglyceridemia
- Hepatic steatosis
- Acanthosis nigricans may be only presenting sign in men
- Primary amenorrhea or oligomenorrhea
- Polycystic ovary disease
- Type A
- Hyperinsulinemia and insulin resistance as a result of mutation in INSR gene (insulin receptor) at 19p13.2

Insulin resistance syndromes

- Type B
- Women of African origin
- >35 years of age
- Auto-antibodies to insulin receptor
- May see paradoxical hypoglycemia (50% mortality)
- Lipoatrophic diabetes has predilection for loss of subcutaneous fat
- HAART therapy

Gestational diabetes mellitus

- 5%–10% of women with gestational diabetes are diagnosed with type 2 diabetes
- Women who have had gestational diabetes have a 35%–60% risk of developing type 2 diabetes in the following 10 to 20 years.
- The risk of subsequent overt type 2 diabetes accumulates over time and the same is likely for cardiovascular disease.
- Are at the risk of developing it again in subsequent pregnancies (41.3%, compared to 4.2% in females without a prior diagnosis).
- Better treated with insulin

Hypoglycemia

- The most common acute metabolic complication in Type 1 or Type 2 diabetes
- Usually as a result of having missed a meal, excessive physical exertion, an excess insulin administration, or during the phase of dose finding for antidiabetic agents.
- The signs and symptoms of hypoglycemia include dizziness, confusion, sweating, palpitations, and tachycardia
- If glucose levels <45mg/dl, may have associated neuronal damage

Mohan, H, Textbook of Pathology, 7th ed., Health Science Publishers. New Delhi. 2015.

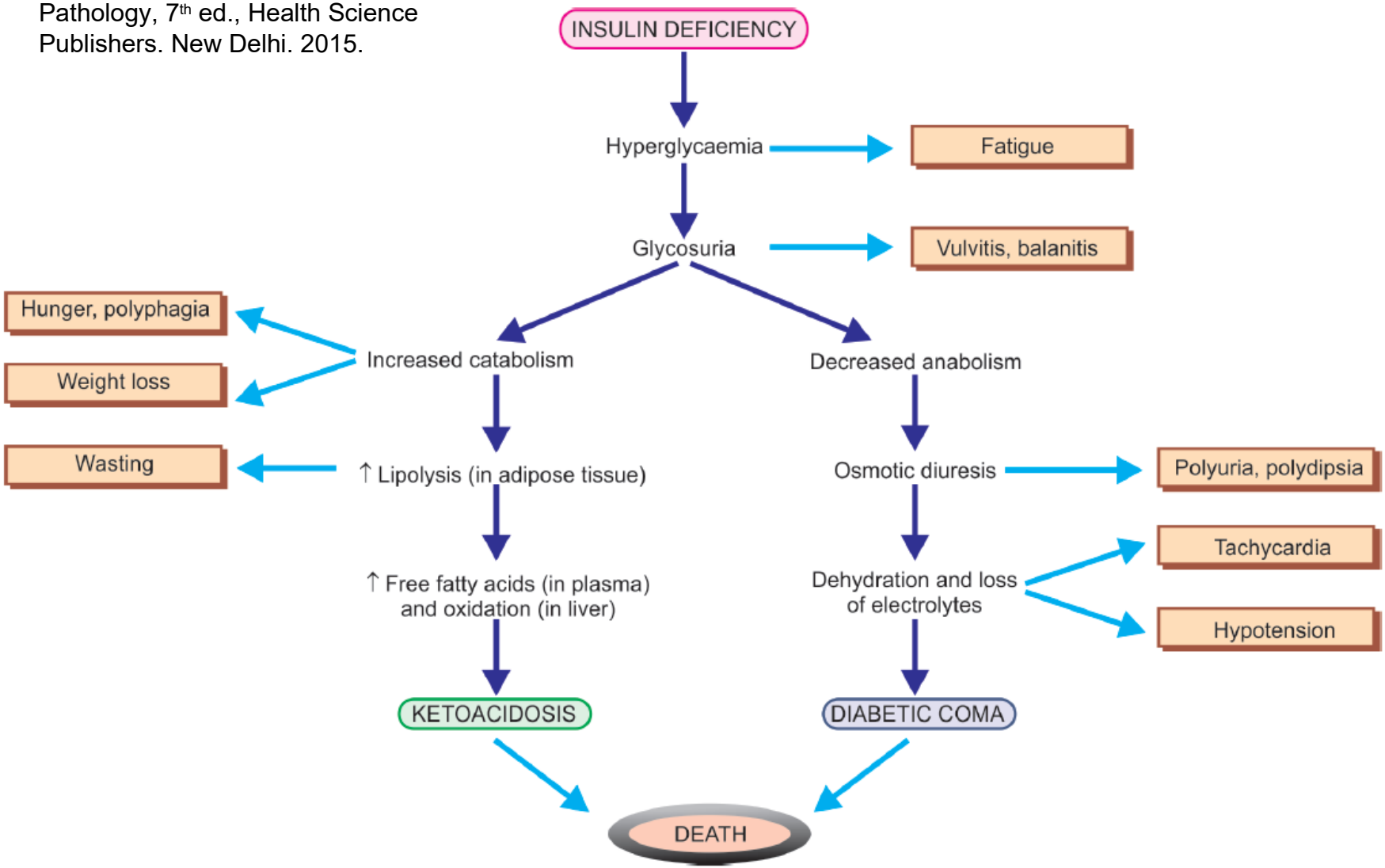


Figure 25.25 Pathophysiological basis of common signs and symptoms due to uncontrolled hyperglycaemia in diabetes mellitus.

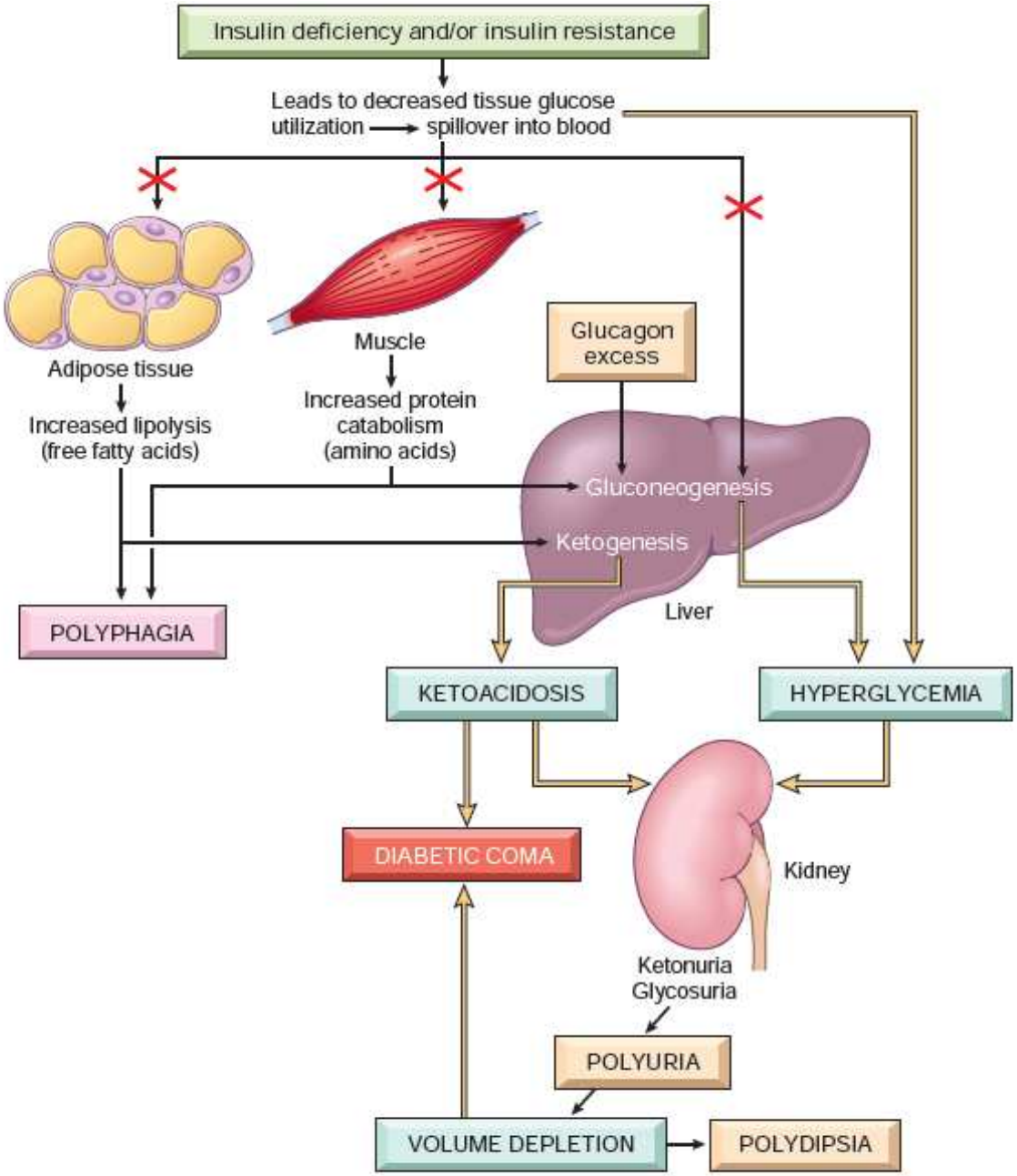


Figure 24-33 Sequence of metabolic derangements underlying the clinical manifestations of diabetes. An absolute insulin deficiency leads to a catabolic state, culminating in ketoacidosis and severe volume depletion. These cause sufficient central nervous system compromise to lead to coma and eventual death if left untreated.

Diabetic ketoacidosis

- Diabetic ketoacidosis may occur in type II diabetes as well as in type I.
- Present with nausea, vomiting, abdominal pain, fruity breath, Kussmaul (deep, shallow) respirations.
- Abdominal pain correlates with severity of acidosis.
- Hyperglycemia present
- Glucose levels may be <350 mg/dL in pregnant women or those with poor oral intake.
- Leukocytosis represents stress (elevated bands if infection)

Diabetic ketoacidosis

- Occurs with insulin deficiency.
- Epinephrine release blocks insulin peripheral action and stimulates glucagon release.
- Gluconeogenesis aggravates hyperglycemia.
- Glycogenolysis aggravates hyperglycemia

Diabetic Ketoacidosis

- Osmotic diuresis leads to significant K^+ losses.
- Dehydration induced hyperaldosteronism aggravates K^+ loss.
- Typical K^+ deficit is 3-5 mEq/kg
- But, hyperkalemia often present,
- Insulin not available to drive K^+ into cells
- Plasma hypertonicity drives H_20 and K^+ from cell into the intravascular compartment
- Acidosis shifts K^+ out of the cells
- Severe dehydration from osmotic diuresis due to hyperglycemia
- H_2O shifts from the intracellular space to intravascular space

Gluconeogensis

- Several amino acids are converted to alanine which is converted to pyruvate.
- Pyruvate in the mitochondrion is dehydrogenated to acetylCoA.
- Vitamin B_1 and Biotin critical
- Oxaloacetate is decarboxylated and combines with AcetylCoA to form citrate
- <u>The rate limiting step in the pathway.</u>

Gluconeogensis

- Citrate is then oxidized and used to generate malate or aspartate to leave the mitochondrion.
- ATP and NADH are regenerated in citrate conversion to α-ketoglutarate to SuccinylCoA.
- Many amino acids enter the Krebs (TCA) cycle at these points.

Ketone body production

- Unrestricted fatty acid mitochondrial oxidation in liver (β-oxidation).
- Exceeds capability of TCA cycle to utilize acetyl CoA
- Diverted to ketone body production in liver with hepatic ketone body production and release.
- Elevated anion gap and absence of urinary ketones should lead to measurement of plasma β-hydroxybutyrate.
- Elevated plasma β-hydroxybutyrate (>1.5 mmol/L) diagnostic

Lactic acidosis

- Lactic acidosis may be present
- Pyruvate accepts H^+ from NADH to form NAD^+.
- NAD+ stores are exhausted in the absence of Oxygen.
- Generates lactate.

Lipid abnormality

- Lipoprotein lipase diminished
- Persistence of chylomicra and VLDL.
- Hypertriglyceridemia noted

Adverse outcomes

- Risk factors for death include:
- Severe coexistent disease
- pH<7.0 at presentation
- >50 units insulin required in first 12 hours
- Glucose >300mg/dl after 12 hours
- Depressed mental status after 12 hours
- Fever after 12 hours
- Mortality rate 1% in those under 55 years of age
- 12% in those over 55 years of aage

Hyperglycemic hyperosmolar non-ketotic coma

- Type II Diabetes (decompensated)
- Some insulin in portal vein limits fatty acid mitochondrial oxidation in liver
- Rarely exceeds capacity to utilize ketone antibodies in peripheral tissues
- May not have ketonuria
- Severe dehydration from osmotic diuresis due to hyperglycemia
- H_2O shifts from the intracellular space to intravascular space.

Hyperglycemic hyperosmolar non-ketotic coma

- Lethargy and obtundation may be seen with plasma osmolality >320 mOsm/L.
- If neurologic changes are present (or persist after therapy)in patients with a serum osmolality <320 mOsm/L, consider neurologic insult
- Mortality rate as high as 15%

Table 25.7 Contrasting features of diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic non-ketotic coma (HHS).

	LAB FINDINGS	DKA	HHS
i.	*Plasma glucose (mg/dL)*	250-600	> 600
ii.	*Plasma acetone*	+	Less +
iii.	*S. Na^+ (mEq/L)*	Usually low	N, ↑ or low
iv.	*S. K^+ (mEq/L)*	N, ↑ or low	N or ↑
v.	*S. phosphorus (mEq/L)*	N or ↑	N or ↑
vi.	*S. Mg^{++}*	N or ↑	N or ↑
vii.	*S. bicarbonate (mEq/L)*	Usually <15	Usually >20
viii.	*Blood pH*	<7.30	> 7.30
ix.	*S. osmolarity (mOsm/L)*	<320	> 330
x.	*S. lactate (mmol/L)*	2-3	1-2
xi.	*S. BUN (mg/dL)*	Less ↑	Greater ↑
xii.	*Plasma insulin*	Low to 0	Some

Mohan, H, Textbook of Pathology, 7th ed., Health Science Publishers. New Delhi. 2015.

Chronic complications

- The morbidity associated with longstanding Type 1 or Type 2 diabetes is due to damage induced in large- and medium-sized muscular arteries (macrovascular disease) and in small vessels (microvascular disease) by chronic hyperglycemia.
- Accelerated atherosclerosis directly related to poor glycemic control (and production of advanced glycation end products).
- Advanced glycation end products (AGE) are formed as a result of non-enzymatic reactions between intracellular glucose derived dicarbonyl precursors with the amino groups of intracellular and extracellular proteins.

Chronic complications

- Polypeptides cross-linked include:
- Collagen I, decreasing elasticity
- Collagen IV, decreasing endothelial cell adhesion
- These resist proteolytic digestion
- Trap interstitial proteins such as LDL.
- Circulating proteins are modified as well.
- AGE binds to a specific receptor (RAGE) expressed on monocytes, T cells, endothelial cells, and smooth muscle.

Pathogenesis

- AGE binding leads to:
- (1) Release of growth factors and inflammatory cytokines from monocytes and macrophages
- (2) Diminished nitric oxide production
- Promotes generation of reactive oxygen species from endothelial cells, resulting in endothelial proliferation and permeability
- (3) Pro-coagulant activity
- Elevated levels of PAI-1, an inhibitor of fibrinolysis
- (4) Promotes proliferation of smooth muscle cells as well as synthesis of extracellular matrix.

Pathogenesis

- Intracellular hyperglycemia stimulates the de novo synthesis of diacylglycerol (DAG) as second messenger with resultant protein kinase C activation
- Leads to reduced fibrinolysis (production of PAI-1), vasoconstriction (production of endothelin-1, depression of nitric oxide synthase), fibrous proliferation (TGF-β production), neovascularization (VEGF production)
- Intracellular hyperglycemia depletes intracellular NAPDH by aldose reductase and limits glutathione regeneration; polyols accumulate (nerves, lenses)

Pathogenesis

- Glucose converted to sorbitol by aldose reductase.
- Sorbitol is converted to fructose by sorbitol dehydrogenase.
- When glucose (and galactose) levels are elevated, this reaction is pushed forward in those tissues where glucose entry is not insulin dependent: lens, nerves, and vessels .
- The conversation to fructose is slow and the increased concentration of sorbitol and galactitol leads to increased osmotic gradient in tissues.
- Cataract formation, glaucoma noted

Pathogenesis

- Hyperglycemia may increase intracellular levels of fructose-6-phosphate
- Serves as substrate for protein glycosylation
- Abnormal expression of PAI-1 and TGF-β

Mohan, H, Textbook of Pathology, 7th ed., Health Science Publishers. New Delhi. 2015.

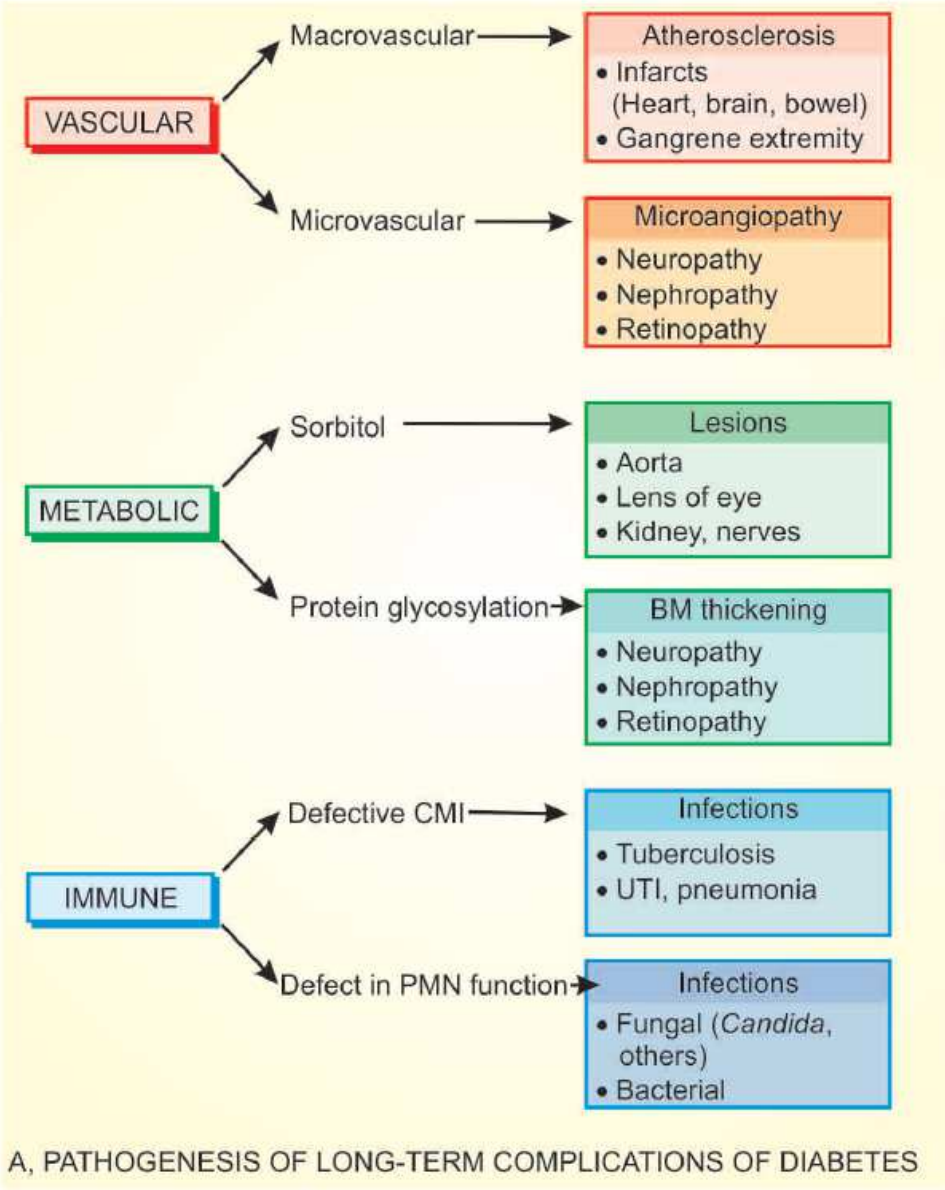
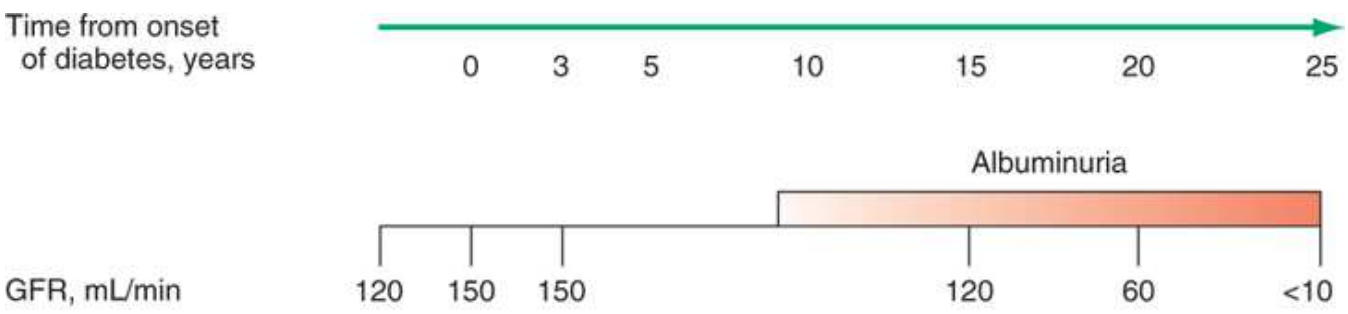


Figure 25.26 Long-term complications of diabetes mellitus. A, Pathogenesis.

Chronic complications of diabetes mellitus

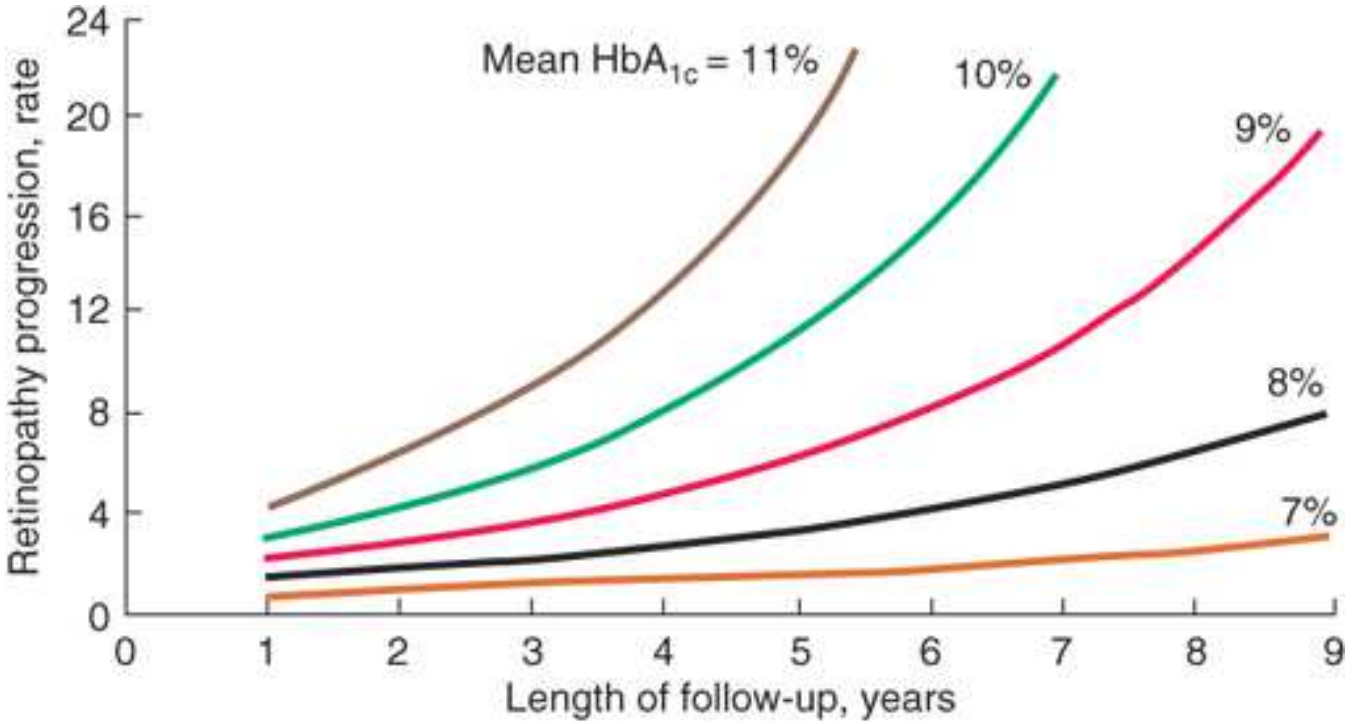
- Capillary basement membrane thickening noted within 2 years of onset of diabetes mellitus. At 5 years, 30% increased thickness.
- Vascular edema leads to smooth muscle cell proliferation and extracellular matrix deposition.
- May see fibrin deposition in capillary loops; in Kidney, at Bowman's capsule as well.
- Microalbuminuria generally presents after 10 years of illness and may precede gross proteinuria by 5 years.



Time course of development of diabetic nephropathy. The relationship of time from onset of diabetes, albuminuria, and the glomerular filtration rate (GFR) are shown.

Chronic complications of diabetes mellitus

- An HbA1c of 7% is associated with a 2% progression of retinopathy at 9 years. At an HbA1c of 8%, 6% progression; at an HbAic of 9%, 20% progression.
- 80% of deaths in type II diabetes mellitus are from cardiovascular disease
- In a study with 7 year follow- up, 15% of diabetics with no history of myocardial infarction died from cardiovascular disease (2% non-diabetics) ; if a prior myocardial infarction, 41% of diabetics died from cardiovascular disease (15%, non-diabetics)



Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J. Loscalzo: Harrison's Principles of Internal Medicine, 20th Edition

Relationship of glycemic control and diabetes duration to diabetic retinopathy. The progression of retinopathy in individuals in the Diabetes Control and Complications Trial is graphed as a function of the length of follow-up with different curves for different hemoglobin A_{1c} (HbA_{1c}) values. (Adapted from The Diabetes Control and Complications Trial Research Group: Diabetes 44:968, 1995.)

Pancreatic neuroendocrine tumors

- Gross pathology:
- May not be encapsulated.
- Histopathology:
- Resemble giant islets.
- Regular cords of monotonous cells oriented to vasculature.
- Carcinomas rare and diagnosed only if metastasize.

Pancreatic neuroendocrine tumors

- α-cell tumors
- Glucagonoma
- Present with
- Mild diabetes mellitus
- Anemia
- Rash (necrolytic migratory erythema)
- Occur most frequently in perimenopausal or post-menopausal women.

.

Pancreatic neuroendocrine tumors

- β-cell tumors
- Insulinoma
- Most common
- Blood glucose <50 mg/dL
- Precipitated by fasting or exercise
- Presents with confusion
- Neuroglycopenia
- Amyloid deposition common in β-cell tumors.
- 10% are carcinomas based on invasion and metastasis

Pancreatic neuroendocrine tumors

- G cell tumors
- Gastrinoma
- May arise in duodenum, pancreas, or peripancreatic tissues.
- 67% of gastrinomas are found in the Zollinger-Ellison triangle bounded by the confluence of the cystic and common bile ducts and the second and third portions of the duodenum.
- Give rise to extreme gastric acid hypersecretion.
- 30% may present with diarrhea
- 25% associated with MEN-1, are multiple.
- Over half are locally invasive.
- Generally have metastasized at presentation.

Pancreatic neuroendocrine tumors

- δ-tumors
- Somatostatinoma
- Associated with:
- Diabetes mellitus
- Steatorrhea
- Hypochlorhydria
- Cholelithiasis.
- Octreide to relieve symptoms

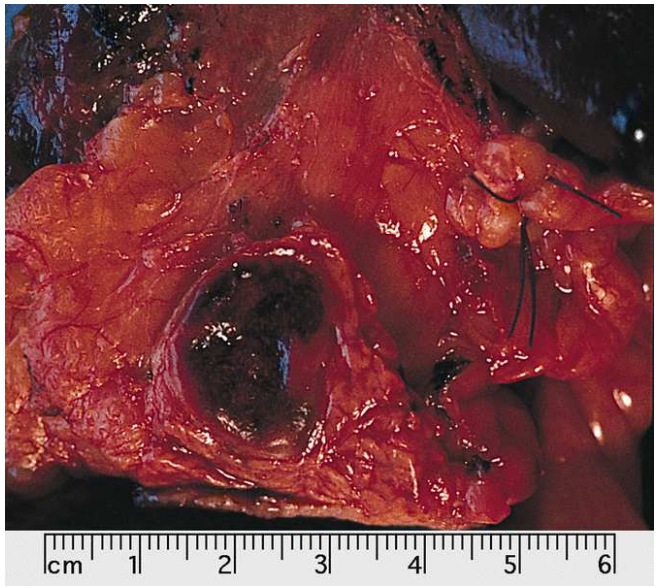
Pancreatic neuroendocrine tumors

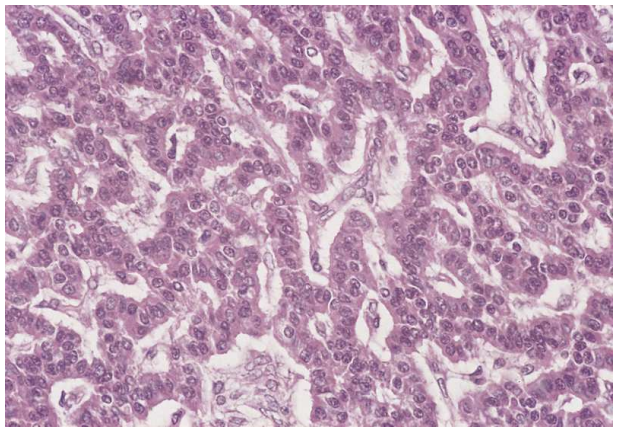
- VIPoma
- May be invasive.
- Presents with:
- Severe watery diarrhea
- Hypokalemia
- Achlorhydria (WDHA syndrome)
- May be associated with neural crest tumors.

Pancreatic neuroendocrine tumors

- Pancreatic carcinoid tumors
- Produce serotonin
- Rare.
- Pancreatic polypeptide-secreting endocrine tumors
- Present as mass lesions
- High plasma levels of this hormone fail to cause symptoms.
- Multihormonal tumors.
- Some pancreatic and extra-pancreatic endocrine tumors produce two or more hormones.
- Not MEN.

Pancreatic neuroendocrine tumor



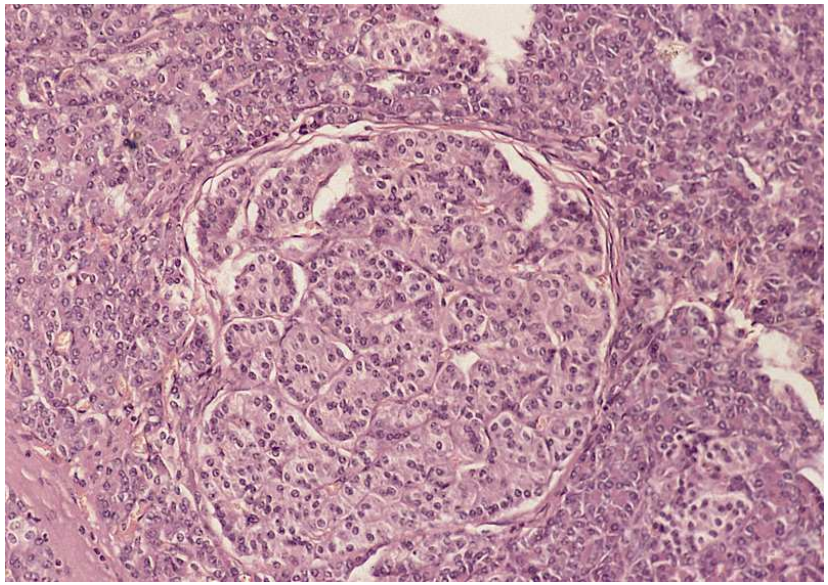


Small (2 cm in diameter) intrapancreatic tumor with expansile margins showing a relatively homogeneous, deep red, hemorrhagic appearance. (Top) Gyriform festoons separated by highly vascular stroma in a clinically nonfunctioning adenoma which was immunohistochemically glucagon- positive. (Bottom)

Figs. 5-3 and 5-8

Solcia, E, Capella, C, Kloppel, G., “Tumors of the Pancreas. Atlas of Tumor Pathology Third Series, Fascicle 20. Armed Forces Institute of Pathology. Washington, D.C. 1997.

Pancreatic neuroendocrine tumor



Islet cell adenoma.
Well-demarcated, partly encapsulated growth of uniform cells forming regular microlobules. Compare with islet in the lower right corner.

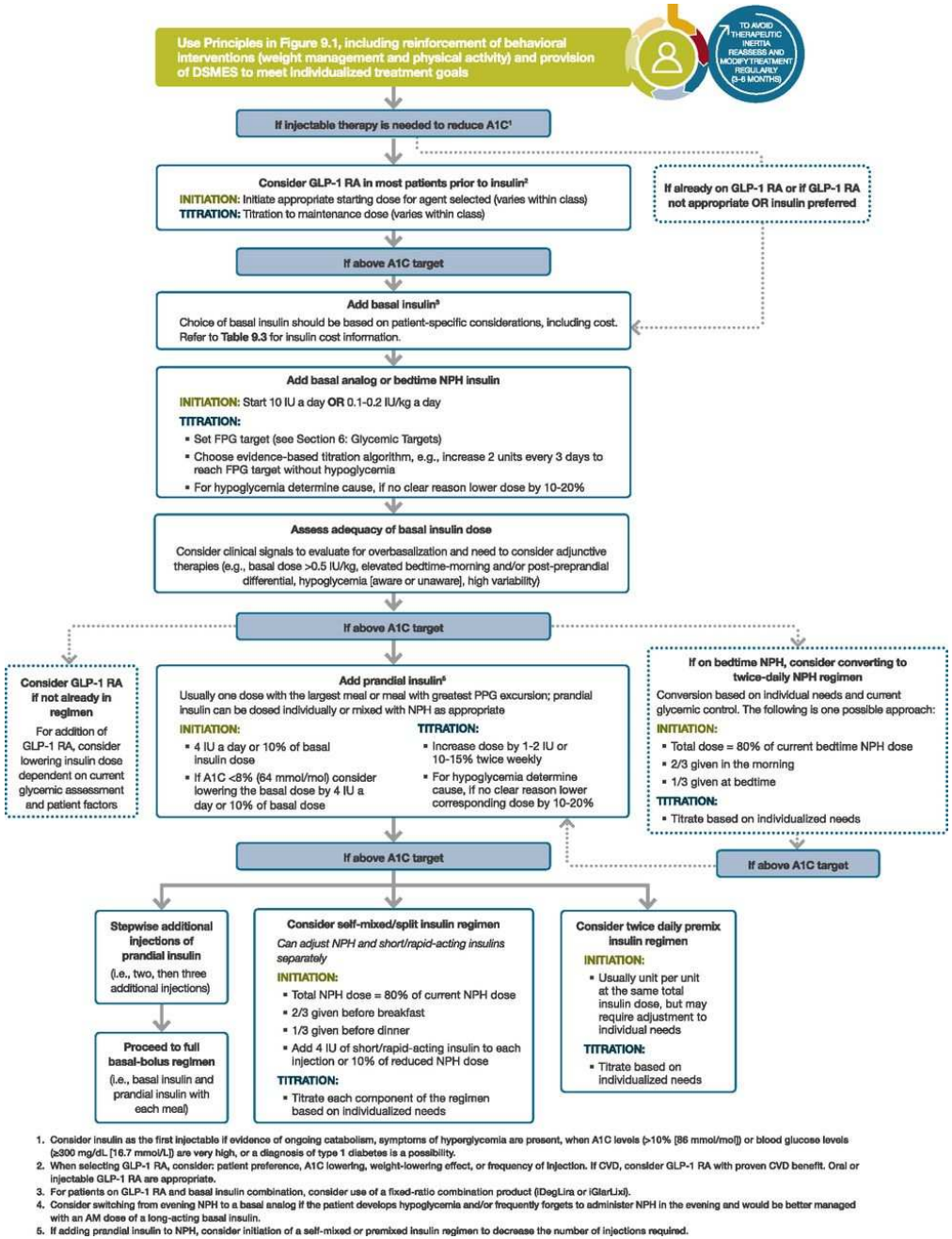
Fig. 5-14

Solcia, E, Capella, C, Kloppel, G., “Tumors of the Pancreas. Atlas of Tumor Pathology Third Series, Fascicle 20. Armed Forces Institute of Pathology. Washington, D.C. 1997.

TREATMENT CONSIDERATIONS

Type I diabetes mellitus

- Intensive therapy with multiple daily injections or continuous subcutaneous insulin infusion reduced Hb A_{1C} and is associated with improved long-term outcomes
- Hypoglycemia more common
- Treatment with analog insulins is associated with less hypoglycemia and weight gain as well as lower A_{1C} compared with human insulins
- Rapidly acting analogs are available
- Pump therapy has marginal advantage



1. Consider insulin as the first injectable if evidence of ongoing catabolism, symptoms of hyperglycemia are present, when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high, or a diagnosis of type 1 diabetes is a possibility.
2. When selecting GLP-1 RA, consider: patient preference, A1C lowering, weight-lowering effect, or frequency of injection. If CVD, consider GLP-1 RA with proven CVD benefit. Oral or injectable GLP-1 RA are appropriate.
3. For patients on GLP-1 RA and basal insulin combination, consider use of a fixed-ratio combination product (iDegLira or iGlarLixi).
4. Consider switching from evening NPH to a basal analog if the patient develops hypoglycemia and/or frequently forgets to administer NPH in the evening and would be better managed with an AM dose of a long-acting basal insulin.
5. If adding prandial insulin to NPH, consider initiation of a self-mixed or premixed insulin regimen to decrease the number of injections required.

American Diabetes Association Diabetes Care 2021 Jan; 44(Supplement 1): S111-S124. https://doi.org/10.2337/dc21-S009

nonpregnant VIEW ALL

1st line **basal-bolus insulin**

Primary options

insulin glargine: injected subcutaneously once daily

or

insulin NPH: injected subcutaneously twice daily

or

insulin detemir: injected subcutaneously twice daily

or

insulin degludec: injected subcutaneously once daily

-- AND --

insulin regular: injected subcutaneously two to three times daily

or

insulin lispro: injected subcutaneously pre-meal

or

insulin aspart: injected subcutaneously pre-meal

or

insulin glulisine: injected subcutaneously pre-meal

OR

pump: uses regular insulin or insulins lispro, aspart, or glulisine

Adjunct ^ pre-meal insulin correction dose

Treatment recommended for SOME patients in selected patient group

A correction dose may be added to the bolus insulin based on the pre-meal blood glucose level. Correction dosing may be calculated as follows when the patient's total daily dose of insulin (TDD) and food intake is stable: 1800/TDD = the predicted point drop in blood glucose per unit of rapid acting insulin. For example, if the TDD is 40 units of insulin, 1800/40 = 45 point drop per unit of insulin.

Example of correction dosing based on pre-meal glucose and above calculation:

45-90 mg/dL (2.2 to 4.9 mmol/L): subtract 1 unit from mealtime insulin

91-135 mg/dL (5.0 to 7.4 mmol/L): add 0 units of correction insulin

136-180 mg/dL (7.5 to 9.9 mmol/L): add 1 unit of correction insulin

181-225 mg/dL (9.9 to 12.4 mmol/L): add 2 units of correction insulin

226-270 mg/dL (12.4 to 14.5 mmol/L): add 3 units of correction insulin

271-315 mg/dL (14.5 to 17.3 mmol/L): add 4 units of correction insulin

316-360 mg/dL (17.4 to 19.8 mmol/L): add 5 units of correction insulin

361-405 mg/dL (19.8 to 22.3 mmol/L): add 6 units of correction insulin

>405 mg/dL (>22.3 mmol/L): add 7 units of correction insulin; call healthcare provider.

The number used to calculate the correction dose may be as low as 1500 or as high as 2200. There are no specific guidelines to determine this number. In general, a lower number should be used for obese, insulin-resistant patients, and a higher number should be used for lean, insulin-sensitive patients.

This correction dose can be added to the patient's mealtime insulin requirement (whether based on general meal size or carbohydrate counting) and given as the total bolus dose.

Adjunct ^ amylin analog

Treatment recommended for SOME patients in selected patient group

Primary options

pramlintide: 15-60 micrograms subcutaneously before each meal

2nd line ^ fixed-dose insulin

Primary options

insulin NPH/insulin regular: (50/50, 70/30) injected subcutaneously twice daily

OR

insulin aspart protamine/insulin aspart: (70/30) injected subcutaneously twice daily

OR

insulin lispro protamine/insulin lispro: (50/50, 75/25) injected subcutaneously twice daily

OR

insulin degludec/insulin aspart: (70/30) injected subcutaneously once or twice daily

Fixed-dose insulin is used when patients are already doing well on a fixed-dose regimen; or cannot manage 3-4 insulin injections daily; or have trouble mixing insulin.

pregnant HIDE ALL

1st line **basal-bolus insulin**

Primary options

insulin NPH: injected subcutaneously twice daily

or

insulin detemir: injected subcutaneously twice daily

-- AND --

insulin regular: injected subcutaneously two to three times daily

or

insulin lispro: injected subcutaneously pre-meal

or

insulin aspart: injected subcutaneously pre-meal

Secondary options

insulin glargine: injected subcutaneously once daily

-- AND --

insulin regular: injected subcutaneously two to three times daily

or

insulin lispro: injected subcutaneously pre-meal

or

insulin aspart: injected subcutaneously pre-meal

OR

pump: uses regular insulin or insulins lispro or aspart

Plus

low-dose aspirin

Treatment recommended for ALL patients in selected patient group

Primary options

aspirin: 60-125 mg orally once daily, usual dose 81 mg/day

Table 1. Pharmacokinetics of SQ insulin preparations*

Insulin	Onset	Peak	Duration
Rapid-acting analogs	5-15 min	1-2 hours	4-6 hours
Regular	30-60 min	2-3 hours	6-10 hours
NPH	2-4 hours	4-10 hours	12-18 hours
Glargine	2 hours	No peak	20-24 hours
Detemir	2 hours	No peak	12-24 hours

* Renal failure leads to prolonged insulin action and altered kinetics

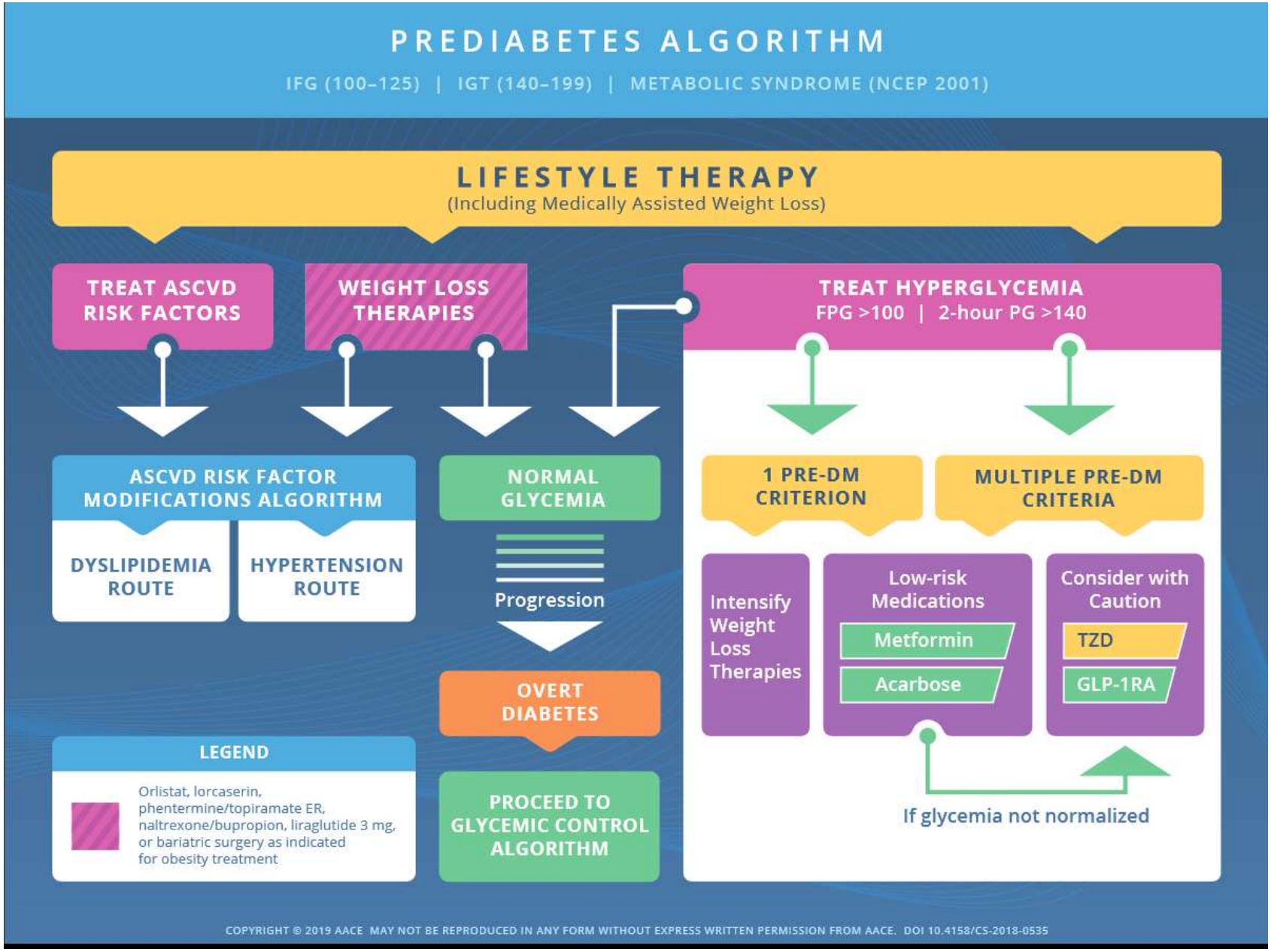
Premixed insulins available include 70/30, Humalog 75/25 and Novolog 70/30 mix, Humalog 50/50. Specialized highly concentrated insulin preparations also are available, such as Lilly U-500.

https://www.jucm.com/management-acute-hyperglycemia-urgent-care-part-1/

PRINCIPLES OF THE AACE/ACE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM

1.	Lifestyle modification underlies all therapy (e.g., weight control, physical activity, sleep, etc.)
2.	Avoid hypoglycemia
3.	Avoid weight gain
4.	Individualize all glycemic targets (A1C, FPG, PPG)
5.	Optimal A1C is ≤6.5%, or as close to normal as is safe and achievable
6.	Therapy choices are affected by initial A1C, duration of diabetes, and obesity status
7.	Choice of therapy reflects cardiac, cerebrovascular, and renal status
8.	Comorbidities must be managed for comprehensive care
9.	Get to goal as soon as possible—adjust at ≤3 months until at goal
10.	Choice of therapy includes ease of use and affordability
11.	A1C ≤6.5% for those on any insulin regimen as long as CGM is being used

 DOI 10.4158/CS-2018-0535



ASCVD RISK FACTOR MODIFICATIONS ALGORITHM

DYSLIPIDEMIA

LIFESTYLE THERAPY (Including Medically Assisted Weight Loss)

LIPID PANEL: Assess ASCVD Risk

STATIN THERAPY
If TG >500 mg/dL, fibrates, Rx-grade omega-3 fatty acids, niacin

If statin-intolerant

Try alternate statin, lower statin dose or frequency, or add nonstatin LDL-C- lowering therapies

Repeat lipid panel; assess adequacy, tolerance of therapy

Intensify therapies to attain goals according to risk levels

RISK LEVELS	HIGH	VERY HIGH	EXTREME
	DESIRABLE LEVELS	DESIRABLE LEVELS	DESIRABLE LEVELS
LDL-C (mg/dL)	<100	<70	<55
Non-HDL-C (mg/dL)	<130	<100	<80
TG (mg/dL)	<150	<150	<150
Apo B (mg/dL)	<90	<80	<70

RISK LEVELS:
- **HIGH:** DM but no other major risk and/or age <40
- **VERY HIGH:** DM + major ASCVD risk(s) (HTN, Fam Hx, low HDL-C, smoking, CKD3,4)*
- **EXTREME:** DM plus established clinical CVD

If not at desirable levels: Intensify lifestyle therapy (weight loss, physical activity, dietary changes) and glycemic control; consider additional therapy

To lower LDL-C:	Intensify statin, add ezetimibe, PCSK9i, colesevelam, or niacin
To lower Non-HDL-C, TG:	Intensify statin and/or add Rx-grade OM3 fatty acid, fibrate, and/or niacin
To lower Apo B, LDL-P:	Intensify statin and/or add ezetimibe, PCSK9i, colesevelam, and/or niacin
To lower LDL-C in FH:**	Statin + PCSK9i

Assess adequacy & tolerance of therapy with focused laboratory evaluations and patient follow-up

* EVEN MORE INTENSIVE THERAPY MIGHT BE WARRANTED ** FAMILIAL HYPERCHOLESTEROLEMIA

HYPERTENSION

GOAL: SYSTOLIC <130, DIASTOLIC <80 mm Hg

ACEi or ARB

For initial blood pressure >150/100 mm Hg:
DUAL THERAPY

ACEi or ARB + Calcium Channel Blocker ✓ / ß-blocker ✓ / Thiazide ✓

If not at goal (2–3 months)

Add calcium channel blocker, ß-blocker or thiazide diuretic

If not at goal (2–3 months)

Add next agent from the above group, repeat

If not at goal (2–3 months)

Additional choices (α-blockers, central agents, vasodilators, aldosterone antagonist)

Achievement of target blood pressure is critical

 DOI 10.4158/CS-2018-0535

Treatment guidelines

- Metformin is the preferred initial pharmacologic agent for the treatment of type 2 diabetes
- The early introduction of insulin should be considered if there is evidence of:
- Ongoing catabolism (weight loss)
- Symptoms of hyperglycemia are present
- When hemoglobin A_{1c} (HbA_{1c}) >10%
- When blood glucose ≥ 300 mg/dL

GLYCEMIC CONTROL ALGORITHM

INDIVIDUALIZE GOALS

A1C ≤6.5% For patients without concurrent serious illness and at low hypoglycemic risk

A1C >6.5% For patients with concurrent serious illness and at risk for hypoglycemia

LIFESTYLE THERAPY (Including Medically Assisted Weight Loss)

Entry A1C <7.5%

MONOTHERAPY[1]

- ✓ Metformin
- ✓ GLP1-RA [2,3]
- ✓ SGLT2i [2,3]
- ✓ DPP4i
- ⚠ TZD
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to Dual Therapy

Entry A1C ≥7.5%

DUAL THERAPY[1]

MET or other 1st-line agent +

- ✓ GLP1-RA [2,3]
- ✓ SGLT2i [2,3]
- ✓ DPP4i
- ⚠ TZD
- ⚠ Basal Insulin
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY[1]

MET or other 1st-line agent + 2nd-line agent +

- ✓ GLP1-RA [2,3]
- ✓ SGLT2i [2,3]
- ⚠ TZD
- ⚠ Basal Insulin
- ✓ DPP4i
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

Entry A1C >9.0%

SYMPTOMS

NO	YES
DUAL Therapy OR TRIPLE Therapy	INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN

Refer to Insulin Algorithm

LEGEND

- ✓ Few adverse events and/or possible benefits
- ⚠ Use with caution

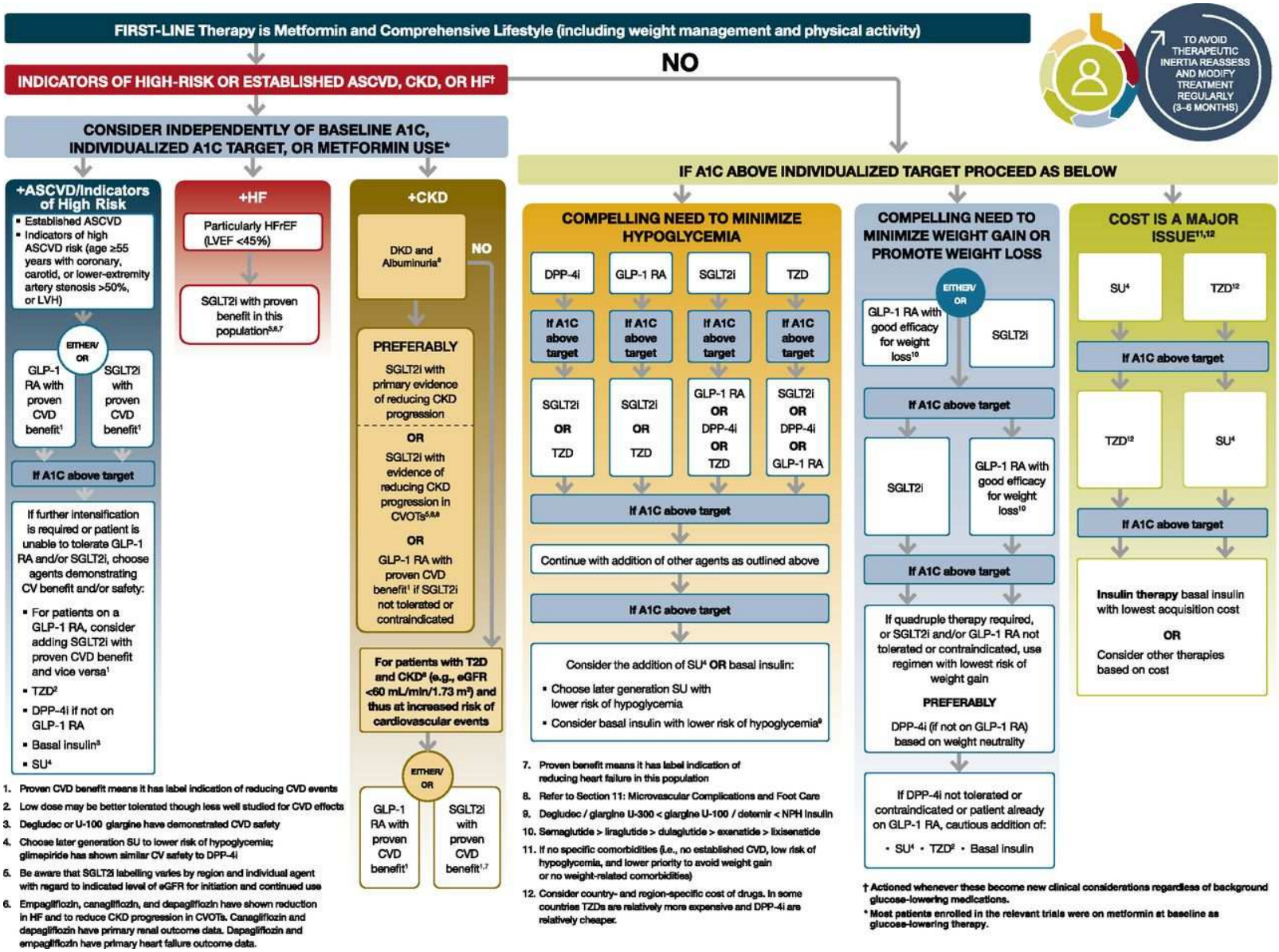
1 Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation

2 Certain GLP1-RAs and SGLT2is have shown CVD and CKD benefits—preferred in patients with those complications

3 Include one of these medications if CHD present

PROGRESSION OF DISEASE

 DOI 10.4158/CS-2018-0535



1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though less well studied for CVD effects
3. Degludec or U-100 glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
5. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure outcome data.
7. Proven benefit means it has label indication of reducing heart failure in this population
8. Refer to Section 11: Microvascular Complications and Foot Care
9. Degludec / glargine U-300 < glargine U-100 / detemir < NPH insulin
10. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
11. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
12. Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4i are relatively cheaper.

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

* Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

ALGORITHM FOR ADDING/INTENSIFYING INSULIN

START BASAL (Long-Acting Insulin)

A1C <8% → **TDD 0.1–0.2 U/kg**

A1C >8% → **TDD 0.2–0.3 U/kg**

Insulin titration every 2–3 days to reach glycemic goal:

- Fixed regimen: Increase TDD by 2 U
- Adjustable regimen:
  - FBG >180 mg/dL: add 20% of TDD
  - FBG 140–180 mg/dL: add 10% of TDD
  - FBG 110–139 mg/dL: add 1 unit
- If hypoglycemia, reduce TDD by:
  - BG <70 mg/dL: 10% – 20%
  - BG <40 mg/dL: 20% – 40%

Consider discontinuing or reducing sulfonylurea after starting basal insulin (basal analogs preferred to NPH)

***Glycemic Goal:**

- <7% for most patients with T2D; fasting and premeal BG <110 mg/dL; absence of hypoglycemia
- A1C and FBG targets may be adjusted based on patient's age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk

Glycemic Control Not at Goal*

INTENSIFY (Prandial Control)

Add GLP1-RA

Or SGLT2i
Or DPP4i

Add Prandial Insulin

Basal Plus 1, Plus 2, Plus 3

- Begin prandial insulin before largest meal
- If not at goal, progress to injections before 2 or 3 meals
- **Start: 10% of basal dose or 5 units**

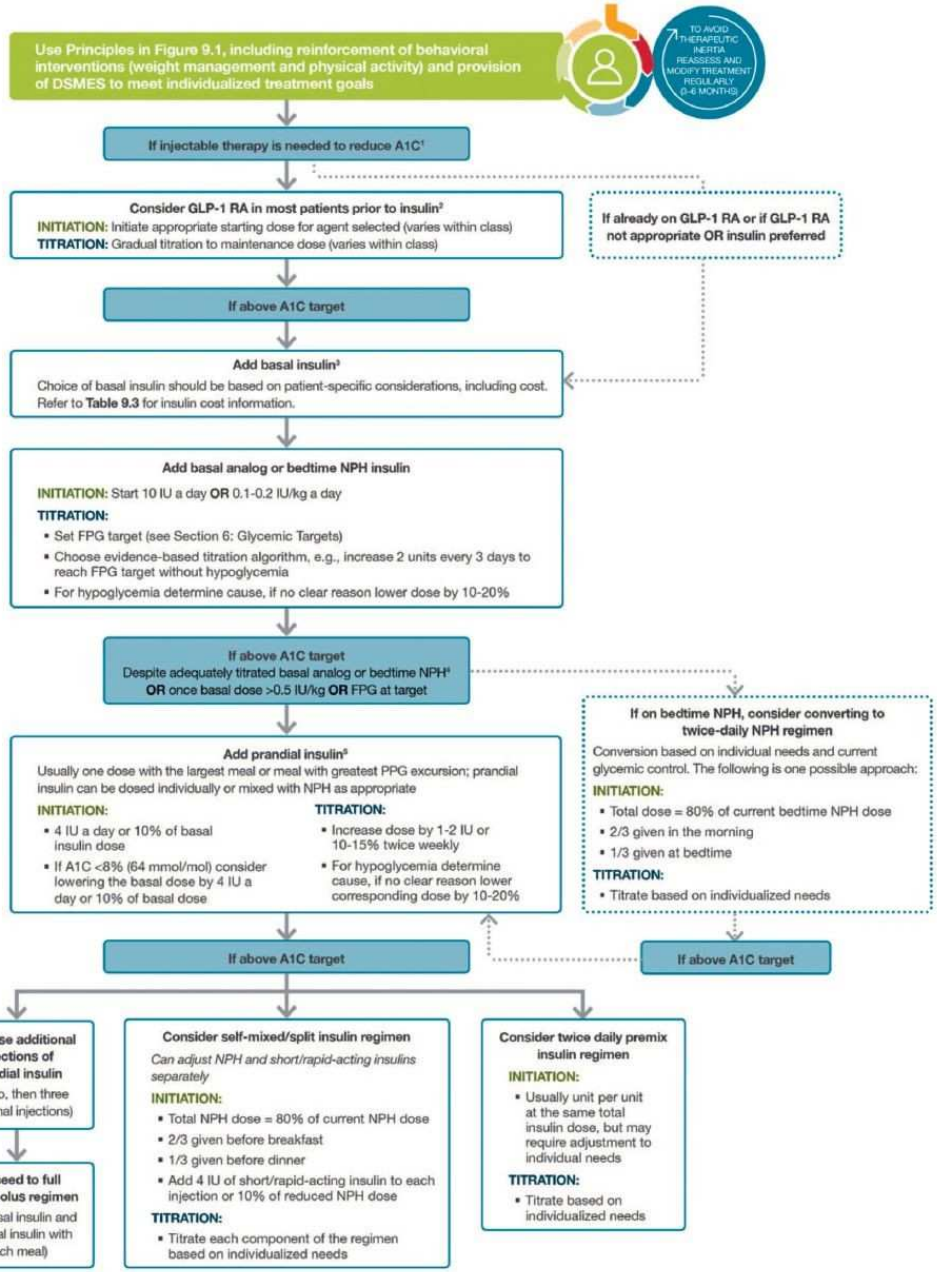
Basal Bolus

- Begin prandial insulin before each meal
- 50% Basal / 50% Prandial TDD 0.3–0.5 U/kg
- **Start: 50% of TDD in three doses before meals**

Insulin titration every 2–3 days to reach glycemic goal:

- Increase prandial dose by 10% or 1-2 units if 2-h postprandial or next premeal glucose consistently >140 mg/dL
- If hypoglycemia, reduce TDD basal and/or prandial insulin by:
  - BG consistently <70 mg/dL: 10% - 20%
  - Severe hypoglycemia (requiring assistance from another person) or BG <40 mg/dL: 20% - 40%

 DOI 10.4158/CS-2018-0535



1. Consider insulin as the first injectable if evidence of ongoing catabolism, symptoms of hyperglycemia are present, when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high, or a diagnosis of type 1 diabetes is a possibility.
2. When selecting GLP-1 RA, consider: patient preference, A1C lowering, weight-lowering effect, or frequency of injection. If CVD, consider GLP-1 RA with proven CVD benefit.
3. For patients on GLP-1 RA and basal insulin combination, consider use of a fixed-ratio combination product (iDegLira or iGlarLixi).
4. Consider switching from evening NPH to a basal analog if the patient develops hypoglycemia and/or frequently forgets to administer NPH in the evening and would be better managed with an AM dose of a long-acting basal insulin.
5. If adding prandial insulin to NPH, consider initiation of a self-mixed or premixed insulin regimen to decrease the number of injections required.

	Efficacy	Hypoglycemia	Weight change	CV effects		Cost	Oral/SQ	Renal effects		Additional considerations
				ASCVD	HF			Progression of DKD	Dosing/use considerations*	
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Low	Oral	Neutral	• Contraindicated with eGFR <30 mL/min/1.73 m²	• Gastrointestinal side effects common (diarrhea, nausea) • Potential for B12 deficiency
SGLT-2 inhibitors	Intermediate	No	Loss	Benefit: empagliflozin†, canagliflozin	Benefit: empagliflozin†, canagliflozin, dapagliflozin‡	High	Oral	Benefit: canagliflozin§, empagliflozin, dapagliflozin	• Renal dose adjustment required (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)	• **FDA Black Box:** Risk of amputation (**canagliflozin**) • Risk of bone fractures (canagliflozin) • DKA risk (all agents, rare in T2DM) • Genitourinary infections • Risk of volume depletion, hypotension • ↑LDL cholesterol • Risk of Fournier's gangrene
GLP-1 RAs	High	No	Loss	Neutral: lixisenatide Benefit: See label indication of reducing CVD events	Neutral	High	SQ; oral (semaglutide)	Benefit: liraglutide	• Renal dose adjustment required (exenatide, lixisenatide) • Caution when initiating or increasing dose due to potential risk of acute kidney injury	• **FDA Black Box:** Risk of thyroid C-cell tumors (**liraglutide, albiglutide, dulaglutide, exenatide extended release**) • Gastrointestinal side effects common (nausea, vomiting, diarrhea) • Injection site reactions • ?Acute pancreatitis risk
DPP-4 inhibitors	Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin	High	Oral	Neutral	• Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment • No dose adjustment required for linagliptin	• Potential risk of acute pancreatitis • Joint pain
Thiazolidinediones	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Low	Oral	Neutral	• No dose adjustment required • Generally not recommended in renal impairment due to potential for fluid retention	• **FDA Black Box:** Congestive heart failure [**pioglitazone, rosiglitazone**] • Fluid retention (edema; heart failure) • Benefit in NASH • Risk of bone fractures • Bladder cancer (pioglitazone) • ↑LDL cholesterol (rosiglitazone)
Sulfonylureas (2nd generation)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	• Glyburide: not recommended • Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	• FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin – **Human insulin**	Highest	Yes	Gain	Neutral	Neutral	Low	SQ; inhaled	Neutral	• Lower insulin doses required with a decrease in eGFR; titrate per clinical response	• Injection site reactions • Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Insulin – **Analogs**						High	SQ			

PROFILES OF ANTIDIABETIC MEDICATIONS

	MET	GLP1-RA	SGLT2i	DPP4i	AGi	TZD (moderate dose)	SU / GLN	COLSVL	BCR-QR	INSULIN	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/Severe / Mild	Neutral	Neutral	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss
RENAL / GU	Contra-indicated if eGFR <30 mL/min/1.73 m^2	Exenatide Not Indicated CrCl <30 Possible Benefit of Liraglutide	Not Indicated for eGFR <45 mL/min/1.73 m^2 Genital Mycotic Infections Possible CKD Benefit	Dose Adjustment Necessary (Except Linagliptin) Effective in Reducing Albuminuria	Neutral	Neutral	More Hypo Risk	Neutral	Neutral	More Hypo Risk	Neutral
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF	Neutral	See #1	See #2	See #3	Neutral	Moderate	Neutral	Neutral	Neutral	CHF Risk	Neutral
CARDIAC ASCVD						May Reduce Stroke Risk	Possible ASCVD Risk	Benefit	Safe	Neutral	
BONE	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral
KETOACIDOSIS	Neutral	Neutral	DKA Can Occur in Various Stress Settings	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

- Few adverse events or possible benefits
- Use with caution
- Likelihood of adverse effects

1. Liraglutide—FDA approved for prevention of MACE events.
2. Empagliflozin—FDA approved to reduce CV mortality. Canagliflozin—FDA approved to reduce MACE events.
3. Possible increased hospitalizations for heart failure with alogliptin and saxagliptin.

DOI 10.4158/CS-2018-0535

Treatment considerations

- Vascular complications of diabetes mellitus may be delayed by tight glucose control.
- Nephropathy risk reduced by 34% in type I diabetes mellitus patients if without retinopathy, 43% if retinopathy
- Intravitreal aflibercept to slow retinopathy
- Nephropathy and retinopathy risk reduced by 16-25% in type II diabetes mellitus patients
- When microalbuminuria develops, little benefit is seen with further aggressive therapy.
- Neuropathy risk reduced by 60%
- There is no indication for loose control.

Treatment considerations

- Diet control reduces relative risk of diabetic progression by 58% (equivalent to drug therapy).
- Protein restriction to 10% of daily calories may slow progression of overt nephropathy.
- Promote 5-10% weight loss and physical exercise (30 min/day).
- International guidelines promote use with ACE inhibitors or Angiotensin Receptor Blockers for the control of hyperglycemia in patients with chronic kidney disease.
- Consider ASA 75mg daily.
- Particularly in pregnant women after the first trimester.

Insulin resistance

- Diagnostic clues
- A waistline over 40 inches in men and 35 inches in women
- Blood pressure readings of 130/80 mmHg or higher
- A fasting glucose level over 100 mg/dL (5.6 mmol/L)
- A fasting triglyceride level over 150 mg/dL (1.7 mmol/L)
- An HDL cholesterol level under 40 mg/dL (1.0 mmol/L) in men and 50 mg/dL (1.3 mmol/L) in women

Insulin resistance treatment

- Time-restricted eating
- Lower HbA_{1c} levels
- Promotes weight loss
- For timed fasting, begin slowly: start with a 12-hour eating window 5 days a week and reduce week-by-week to an 8-hour eating window 7 days a week.
- This eating window can be shortened to 4 hours or less over time.
- The ideal is a 1-2 hour eating window restricted to one meal a day.
- Timed fasting can be interspersed with 36-to 48-hour fasts.

Insulin resistance treatment

- Low-carbohydrate (ketogenic) diet
- Aim for a diet high in saturated fat, mono-unsaturated fat, and Omega-3 fatty acids.
- The carbohydrate content of a meal should not exceed 25 grams.
- Magnesium
- Probiotics with Bifidiobacterium
- 30 minutes mild exercise daily

Insulin resistance treatment

- Metformin
- Decreases intestinal glucose absorption
- Improves peripheral glucose uptake
- Lowers fasting plasma insulin levels
- Increases insulin sensitivity
- Result in a reduction of blood glucose concentrations without causing overt hypoglycemia

Insulin resistance treatment

- Berberine
- Quaternary ammonium salt from the protoberberine group of isoquinoline alkaloids found in a number of different plants.
- Inhibits the voltage-gated K+ channels of pancreatic β cell membrane
- Promotes insulin secretion without causing hypoglycemia
- Stimulates glycolosis
- Inhibits gluconeogenesis and adipogenesis in the liver
- Lowers testosterone.

Management of diabetic ketoacidosis

	Mild DKA	Moderate DKA	Severe DKA
Arterial pH	7.25–7.3	7.0 to <7.24	<7.0
Serum bicarbonate (mmol/L)	15–18	10 to <15	<10
Anion gap	>10	>12	>10
Mental status	Alert	Alert/drowsy	Stupor/coma

Adapted from American Diabetes Association 2009 consensus statement. In all cases, plasma glucose is >14 mmol/L (>250 mg/dL), urine, and serum ketones are positive and effective osmolality is variable.

Maintain glucose between 140-180mg/dL after insulin therapy initiated

DIABETIC KETOACIDOSIS FLOW-CHART (ADULTS / AUSTIN HEALTH)

**** Contact Endocrinology about all patients with DKA ****

Austin Health

Evaluation: Search for precipitant is key

1. HYDRATION

Fluid deficit: ~100mL/kg (7L in 70kg man)
Assess:

- Fluid state
- Comorbidities (i.e. cardiac / renal function)
- Response to fluids

<18 years of age (Especially if <70kg)
Refer to the Royal Children's Hospital Guideline and discuss with the Paediatric Endocrinology team:
http://www.rch.org.au/clinicalguide/guideline_index/Diabetes_Mellitus/

Shock

- Commence hydration
- **Discuss with ICU**

Hypovolaemia

FLUIDS	Recommended RATES
Litre 1	**Stat (not through a pump)** **No** potassium added Give while waiting for biochemistry results
Litre 2	**1 hour** Need biochemistry results for IVT selection
Litre 3	**2 hours**
Litre 4+	**4-8 hours** Depending on volume state / renal function

Wards: 0.9% Normal Saline preferred
ED: Balanced Electrolyte Solutions / Plasmalyte preferred
Exceptions:

- Corrected Sodium ≥150mmol/L: As directed by Endocrinology / ICU (likely 0.45% N.Saline)

2. POTASSIUM

URGENT Venous Blood Gas (VBG) result
Total K+ deficit: ~3-5mmol/L/kg

Special patients (risk hyperkalaemia):
Anuric renal failure
Chronic renal failure
Hyperkalaemia on presentation

- **'Recommended rates' do not apply**
- Individualised with Endocrinology plus other specialty units (i.e. ICU / Renal)

Serum Potassium	Recommended RATES	Caution
<4.0 mmol/L	20 mmol/hour	Advise cardiac monitoring (*Not suitable for general ward transfer*)
4.0-5.5mmol/L	10 mmol/hour	
>5.5 mmol/L	Nil	
Replacement: 10mmol KCl in 100mL 0.9% N.Saline **Cardiac Monitoring**: ED / ICU / HDU		

MONITOR Potassium:

- Initially: VBG 1 hourly
- When stable (4.0-5.5): VBG every 2-4 hours

Volume expansion commenced (Litre 1)
AND
Potassium >3.5mmol/L

3. INSULIN

Bolus: ActRapid 0.1U/kg IV

- IF initial insulin rate is **<0.14U/kg/hour**

Basal:

- Give patients' regular sub/cut basal insulin (i.e. lantus / protaphane) **even while on IV insulin infusion**
- Endocrinology may also commence basal insulin for patients not previously prescribed.

INSULIN INFUSION RATES

BSL (mmol/L)	Standard (units)	Adjusted (units)
0-4	0 (and notify)	0 (and notify)
4.1-6	0.5	1
6.1-8	1	2
8.1-12	2	3
12.1-16	3	5
16.1-20	5	7
>20	7	10

Adjusted rate used only **IF DIRECTED BY ENDOCRINOLOGY TEAM** (i.e. response inadequate)

4. DEXTROSE

When BSL ≤15mmol/L
ADD
5% Dextrose: 12 hourly rate
DO NOT CEASE once started

https://www.frontiersin.org/files/Articles/248109/fendo-08-00106-HTML-r1/image_m/fendo-08-00106-g003.jpg

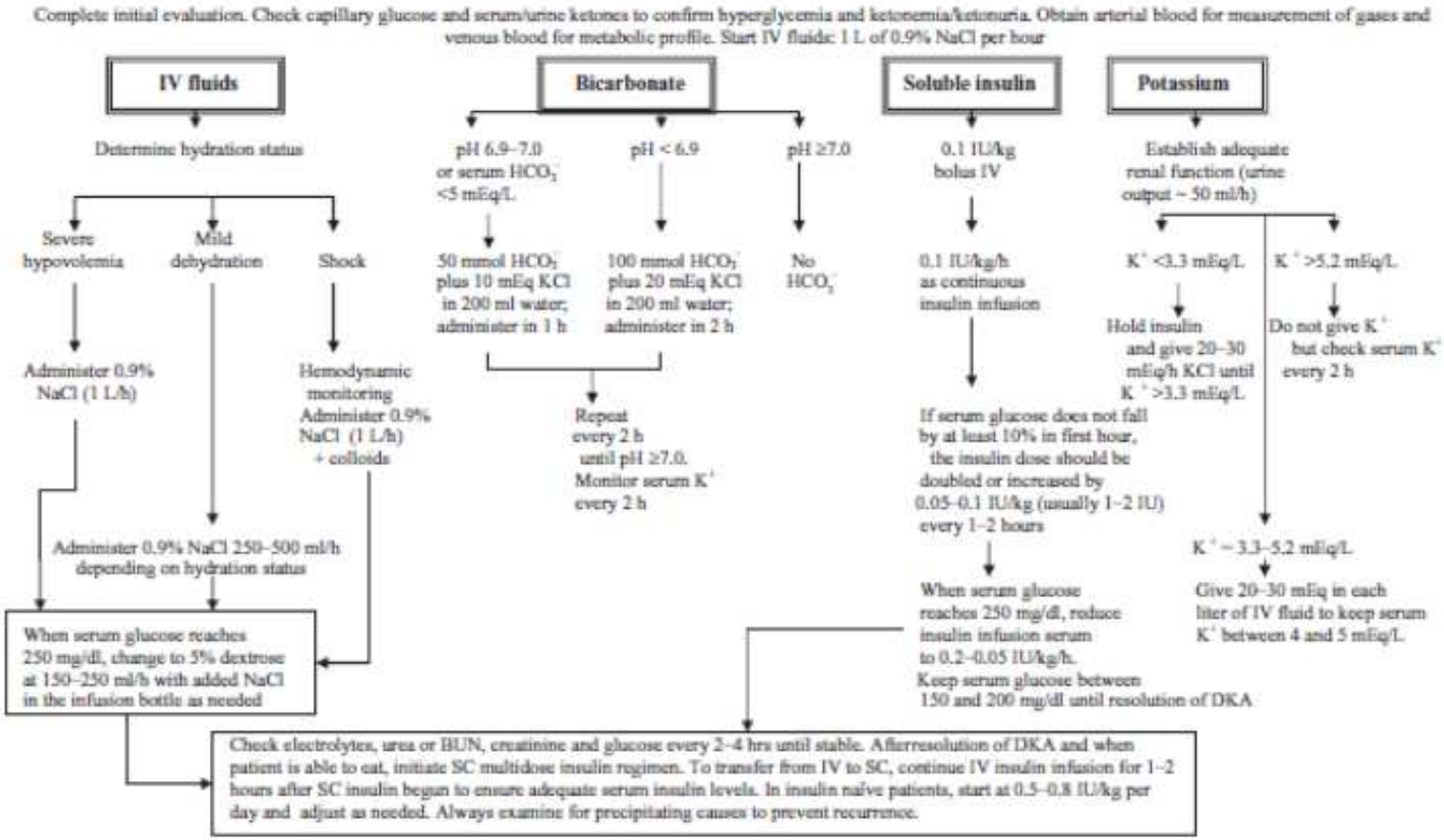


Figure 1.2 Proposed algorithm for the treatment of diabetic ketoacidosis (Modified from Reference 9).

http://www.diabetesincontrol.com/diabetic-emergencies-diabetic-ketoacidosis-in-adults-part-4/

Outcomes

- In diabetic patients at low cardiovascular risk, no treatment differs from placebo for vascular outcomes.
- In patients at increased cardiovascular risk receiving metformin-based background therapy, sodium–glucose cotransporter-2 (SGLT-2) inhibitors reduced heart failure hospitalization and end-stage renal disease.

Outcomes

- In patients at increased cardiovascular risk receiving metformin-based background therapy, oral empagliflozin, dapagliflozin, semaglutide, liraglutide, and extended-release exenatide, reduced all-cause mortality.
- Oral semaglutide, liraglutide, and empagliflozin, also reduced cardiovascular death.
- Odds of stroke were lower with subcutaneous semaglutide and dulaglutide.
- But, subcutaneous semaglutide and canagliflozin increased diabetic retinopathy and amputation, respectively.