**DIABETES**

**Hyperglycemic Crises** - Slides

***CLINICAL PRESENTATIONS*** *– signs & symptoms*

**DEFINITIONS:**

Diabetes Mellitus

A group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both

A group of metabolic disorders characterized by [hyperglycemia](javascript:PopupGlossaryTerm(2752285);). It is associated with abnormalities in carbohydrate, fat, and protein metabolism and results in chronic complications including microvascular, macrovascular, and neuropathic disorders.

* Hyperglycemic crises
  + Diabetic ketoacidosis (DKA)
  + Hyperglycemic hyperosmolar state (HHS)

**Diabetic ketoacidosis** (**DKA**) is a potentially life-threatening complication in patients with [diabetes mellitus](http://en.wikipedia.org/wiki/Diabetes_mellitus). It happens predominantly in those with [type 1 diabetes](http://en.wikipedia.org/wiki/Diabetes_mellitus_type_1), but it can occur in those with [type 2 diabetes](http://en.wikipedia.org/wiki/Diabetes_mellitus_type_2) under certain circumstances. DKA results from a shortage of [insulin](http://en.wikipedia.org/wiki/Insulin); in response the body switches to burning [fatty acids](http://en.wikipedia.org/wiki/Fatty_acid) and producing acidic [ketone bodies](http://en.wikipedia.org/wiki/Ketone_bodies) that cause most of the symptoms and complications

**Hyperglycemic hyperosmolar state (HHS)** Hyperosmolar hyperglycemic state is a life-threatening emergency manifested by marked elevation of blood glucose, hyperosmolarity, and little or no ketosis. Although the precipitating causes are numerous, underlying infections are the most common. Other causes include certain medications, non-compliance, undiagnosed diabetes, substance abuse, and coexisting disease. Physical findings of hyperosmolar hyperglycemic state include those associated with profound dehydration and various neurologic symptoms such as coma.

TABLE 1  
**Comparison of Diabetic Ketoacidosis to Hyperosmolar Hyperglycemic State**

|  | ***Diabetic ketoacidosis*** |  | |
| --- | --- | --- | --- |
| ***Variables*** | ***Mild*** | ***Moderate*** | ***Severe*** | ***Hyperosmolar hyperglycemic state*** |
| Plasma glucose leve (mg per dL [mmol per L]) | >250 (13.9) | >250 | >250 | >600 (33.3) |
| Arterial pH level | 7.25 to 7.30 | 7.00 to 7.24 | <7.00 | >7.30 |
| Serum bicarbonate level (mEq per L) | 15 to 18 | 10 to < 15 | <10 | >15 |
| Urine or serum ketones | Positive | Positive | Positive | Small or negative |
| Effective serum osmolality (mOsm per kg) | Variable | Variable | Variable | >320 |
| Anion gap | >10 | >12 | >12 | Variable |
| Alternative sensoria in mental obtundation | Alert | Alert, drowsy | Stupor, coma | Stupor, coma |

Signs and symptoms:

1. Classic 3 P’s – POLYURIA – POLYDIPSIA - POLYPHAGIA
2. Fatigue and weight loss
3. Recurrent respiratory, vaginal, or other infections
4. Blurred vision
5. Ketoacidosis or Hyperglycemic Hyperosmolar NonKetotic Syndrome

**Polyuria** is a condition usually defined as excessive or abnormally large production or passage[[1]](http://en.wikipedia.org/wiki/Polyuria" \l "cite_note-0) of [urine](http://en.wikipedia.org/wiki/Urine) (at least 2.5[[2]](http://en.wikipedia.org/wiki/Polyuria#cite_note-1) or 3[[3]](http://en.wikipedia.org/wiki/Polyuria#cite_note-merck-2) L over 24 hours in adults).

**Polydipsia** is a medical symptom in which the patient displays excessive [thirst](http://en.wikipedia.org/wiki/Thirst)

**Polyphagia** (sometimes known as **hyperphagia**) is a [medical sign](http://en.wikipedia.org/wiki/Medical_sign) meaning excessive [hunger](http://en.wikipedia.org/wiki/Hunger) and abnormally large intake of solids by mouth.

Clinical presentations of DM – from lecture handout

Hyperglycemia:

* + Absolute or relative insulin deficiency
  + DKA > 250 mg/dl
  + HHS > 600 mg/dl

Dehydration, thirst, polyuria

* + Caused by osmotic diuresis
  + Water loss, hypovolemia
  + Decrease GFR
  + PE: loss of skin turgor, dry mucous membranes, tachycardia, hypotension

Metabolic acidosis

* + pH decreases (< 7.35)
  + HCO3 decreases (< 22)
  + PaCO2 normal
  + Nausea/vomiting
  + Abdominal pain
  + Fruity breath odor

Positive anion gap

* MULEPA**K** - Methanol, Uremia, Lactate, Ethylene glycol, Paraldehyde, ASA, Ketoacidosis
  + AG = Na – (Cl + HCO3)
  + Usually in DKA

The **anion gap** is the difference in the measured [cations](http://en.wikipedia.org/wiki/Cations) and the measured [anions](http://en.wikipedia.org/wiki/Anions) in [serum](http://en.wikipedia.org/wiki/Blood_serum), [plasma](http://en.wikipedia.org/wiki/Blood_plasma), or [urine](http://en.wikipedia.org/wiki/Urine).

A normal anion gap is often defined as being within the [prediction interval](http://en.wikipedia.org/wiki/Prediction_interval) of 3–11 mEq/L,[[4]](http://en.wikipedia.org/wiki/Anion_gap" \l "cite_note-Archives_of_Internal_Medicine-3) with an average estimated at 6 mEq/L

<http://en.wikipedia.org/wiki/Anion_gap>

Rapid deep respirations (Kussmaul)

* + Compensatory response

Hyperosmolality

* + Normal: 280 -295 mOsm/kg water
  + P osm= 2 Na + (gluc/18 ) + (BUN/2.8)

Plasma osmolality: number of particles in the medium

Effective osmole: solute unable to cross the semipermeable cell membrane

* + - **Na+** (can travel freely between ICF and ECF but is contained to the ECF by the Na/K ATPase and so can cause water diffusion)
    - Glucose
    - intracellular K+

Ineffective osmole: solute that does Not cause water movement across membranes so can contribute to osmolality but does NOT contribute to tonicity

* + - **Urea** (able to cross cell membranes so unable to translocate water)

Plasma osmolality - sum of the osmolalities of the individual solutes in the plasma

Primary solutes - Na+, Cl-, urea, glucose, other anions/cations, plasma proteins

Coma

* + Due to hyperosmolality
  + Glasgow Coma Score

**Glasgow Coma Scale** or **GCS** is a [neurological](http://en.wikipedia.org/wiki/Neurology) [scale](http://en.wikipedia.org/wiki/Scale_(ratio)) that aims to give a reliable, objective way of recording the conscious state of a person for initial as well as subsequent assessment. A patient is assessed against the criteria of the scale, and the resulting points give a patient score between 3 (indicating deep unconsciousness) and either 14 (original scale) or 15 (the more widely used modified or revised scale).

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Glasgow Coma Scale | | | | | | | |
|  | **1** | **2** | | **3** | **4** | **5** | **6** |
| **Eyes** | Does not open eyes | Opens eyes in response to painful stimuli | Opens eyes in response to  voice | | Opens eyes spontaneously | N/A | N/A |
| **Verbal** | Makes no sounds | Incomprehensible sounds | Utters inappropriate words | | Confused, disoriented | Oriented, converses normally | N/A |
| **Motor** | Makes no movements | Extension to painful stimuli ([decerebrate response](http://en.wikipedia.org/wiki/Abnormal_posturing#Decerebrate)) | Abnormal flexion to painful stimuli ([decorticate response](http://en.wikipedia.org/wiki/Abnormal_posturing#Decorticate)) | | Flexion / Withdrawal to painful stimuli | Localizes painful stimuli | Obeys commands |

The scale comprises three tests: [eye](http://en.wikipedia.org/wiki/Visual_perception), [verbal](http://en.wikipedia.org/wiki/Speech_communication) and [motor](http://en.wikipedia.org/wiki/Motor_skill) responses. The three values separately as well as their sum are considered. The lowest possible GCS (the sum) is 3 (deep [coma](http://en.wikipedia.org/wiki/Coma) or [death](http://en.wikipedia.org/wiki/Death)), while the highest is 15 (fully awake person).

Hyperlipidemia

Elevated WBC

Electrolyte disturbances

* + Sodium: decreased, normal, or elevated
    - Osmolar dilution decreases Na levels
    - Corrected Na: add 1.6 mEq sodium for each 100 mg plasma glucose >100mg/dl
    - *Example*: BG = 500mg/dl, Na = 130 mEq/L
    - Corrected Na = 1.6 (4) + 130
    - Corrected Na = 136.4 = **136 mEq/L**

ACID-BASE Balance

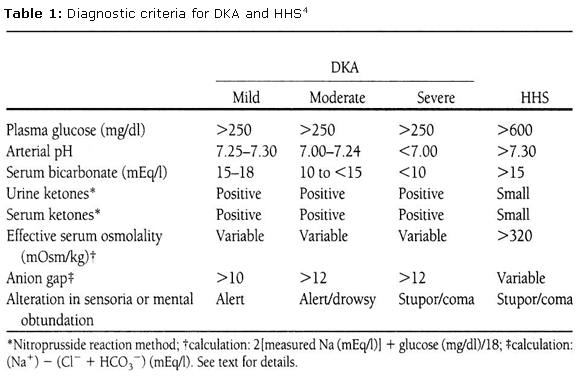
|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **pH** | **PaCO2** | **HCO3** | **Compensation**  **PaCO2** |
| Metabolic acidosis | decrease | NL | decrease | decrease |
| Metabolic alkalosis | increase | NL | increase | increase |
| Respiratory acidosis | decrease | increase | NL | increase |
| Respiratory alkalosis | increase | decrease | NL | decrease |

***DIAGNOSIS***

Diagnostic procedures

* History and physical exam
  + DKA develops < 24 hr
  + HHS develops over several days to weeks
* Laboratory evaluation
  + Chem 7 (electrolytes, BG, and BUN/SCr)
  + ABG (arterial blood gas – oxygen and carbon dioxide)
  + CBC with differential (complete blood count)
  + Osmolality
  + ketones
* EKG

Diagnostic criteria



***ETIOLOGY*** *– cause & origin*

***PATHOPHYSIOLOGY*** *– essential nature*

**Diabetes Pathophysiology**– Lecture Handout

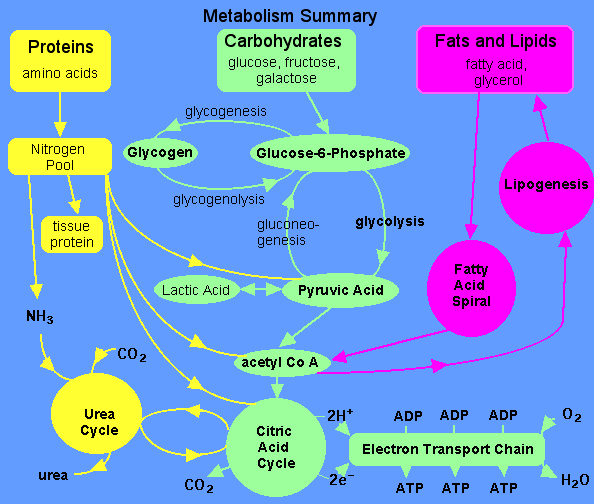
Pathophysiology:

* Reduction of circulating insulin
* Elevation of counterregulatory hormones (glucagon, cathecolamines, cortisol, and growth hormone)
* The ketoacids formed in DKA are
  + ß hydroxybutyric acid
  + acetoacetic acid

Precipitating factors:

* Non compliance with insulin
* Infection (50%)
* New onset DM type 1
* CVA (cerebro-vascular accidents)
* Trauma
* Pulmonary embolism
* Myocardial infarction
* Alcohol abuse
* Drugs (corticosteroids, pentamidine, sympathomimetics, adrenergic agents, diuretics)

**Metabolism and Utilization of Carbohydrates, Proteins, and Fats**



Carbohydrates are metabolized to glucose

Glucose is absorbed from the GI tract into the bloodstream (where it is oxidized in skeletal muscle to produce energy)

Glucose is also stored in the liver: glycogen

Converted in adipose tissue to fats and triglycerides

**Insulin**

Insulin is produced in, stored in, and released

(0.5 to 1 Unit/hour) from beta cells in the pancreas

Increases uptake of glucose by tissues, increases liver Cleared metabolically by the liver,

glycogen levels, decreases glycogen breakdown by the liver, peripheral tissues, and kidneys

increases synthesis of fatty acids, decreases breakdown of fatty

acids into ketone bodies, and promotes incorporation of amino

acids into proteins

Glucose Utilization

Normal glucose concentration: 40 – 160 mg/dl Plasma concentrations > 180 mg/dl

(BG level of 40 mg/dl needed for brain functions)

Exceed renal tubular reabsorption rate

Diffuses into the brain Can only get into other

Without the aid of insulin body cells with the aid of insulin Glucose spills into urine

Glucose deprivation to cells

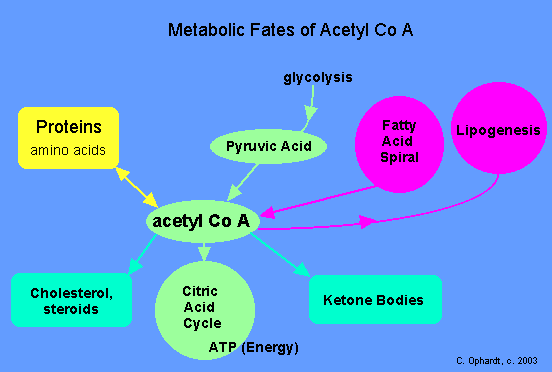
Muscle and adipose tissue will convert

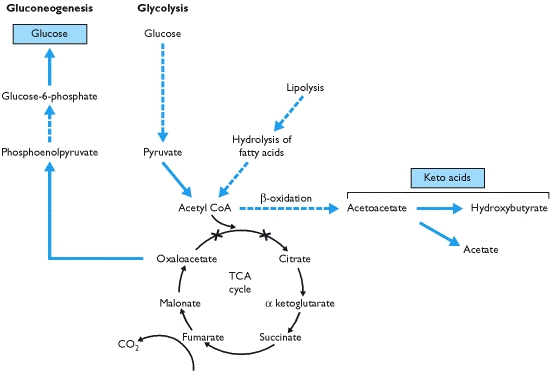
amino acids and fatty acids to carbohydrates

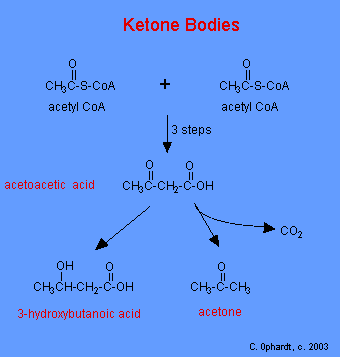
Continued deprivation: tissues metabolize stored fats

Production of free fatty acids

Oxidized to ketone bodies







When the body is deprived of food whether by voluntary or involuntary fasting, starvation is the net result. During starvation, glycogen reserves are rapidly depleted and the body begins to metabolize reserves of fat and protein.

The entry of acetyl CoA into the citric acid cycle depends on the availability of oxaloacetic acid for the formation of citric acid. In starvation or uncontrolled diabetes situations, oxaloacetic acid is used to synthesize glucose and is then not available for use with acetyl CoA. Under these conditions, acetyl CoA is diverted from the citric acid cycle to the formation of acetoacetic and 3-hydroxybutanoic acids.

In three steps, two acetyl CoA react to make acetoacetic acid.

The acetoacetic acid may be changed into either acetone or 3-hydroxybutanoic acid.

All three compounds are collectively known as **ketone bodies** even though one is not a ketone.

The odor of acetone may be detected on the breath of a person with excess ketone bodies in the blood. The overall accumulation of ketone bodies in blood and urine is known as **ketosis.** The acids also upset buffers in the blood to cause **acidosis**.

Both acetoacetic acid and 3-hydroxybutanoic acid can be used by the heart, kidneys, and brain for metabolism to produce energy. The heart and kidneys actually prefer these to glucose. In contrast, the brain prefers glucose, but will adapt if necessary in starvation or diabetic conditions.

**AMYLIN**



Amylin functions as part of the [endocrine](http://en.wikipedia.org/wiki/Endocrine) [pancreas](http://en.wikipedia.org/wiki/Pancreas) and contributes to [glycemic control](http://en.wikipedia.org/wiki/Glycemic_control). The peptide is secreted from the pancreatic islets into the blood circulation and is cleared by peptidases in the kidney. It is not found in the urine.

Amylin's metabolic function is now somewhat well characterized as an inhibitor of the appearance of nutrient [especially glucose] in the plasma.[[6]](http://en.wikipedia.org/wiki/Amylin#cite_note-Pittner_RA.2C_Albrandt_K.2C_Beaumont_K.2C_et_al._1994_19.E2.80.9328-5) It thus functions as a synergistic partner to [insulin](http://en.wikipedia.org/wiki/Insulin), with which it is cosecreted from pancreatic beta cells in response to meals. The overall effect to slow the rate of appearance (Ra) of glucose from the meal is accomplished via coordinate slowing down gastric emptying, inhibition of digestive secretion [gastric acid, pancreatic enzymes, and bile ejection], and a resulting reduction in food intake.

**Glucagon-like-peptide-1(GLP-1)**

* + Secreted by the small intestines in response to food intake
  + Binds to receptors in the beta cells of the pancreas
  + Has a very short half life
  + Enhances glucose dependent insulin secretion, suppresses inappropriate glucagon secretion, delays gastric emptying, and reduces food intake

**DPP-IV**

**Dipeptidyl peptidase-4** (**DPP4**), also known as **adenosine deaminase complexing protein 2** or **CD26**

* + Enzyme that breaks down GLP-1
  + If you inhibit this enzyme:
    - Enhances glucose dependent insulin secretion, suppresses inappropriate glucagon secretion, delays gastric emptying, and reduces food intake

Active GLP-1

DPP-IV

Inactive GLP-1

**Types of Diabetes**

1. **Type 1**:
2. Results from an auto immune attack on the beta islet cells
3. Environmental triggers
4. **Type 2**:
5. Results from pancreatic defect, insulin resistance in both liver and peripheral tissues, and/or persistent hepatic glucose production
6. **Gestational**:
7. Carbohydrate intolerance of varying degrees of severity with onset or first recognition during pregnancy
8. **Secondary**:
9. Pancreatic disease
10. Endocrinopathies
11. Drug-induced

**Classifications:** (Use the assigned reading to complete the following table)

<http://books.google.com/books?id=oEvE_OAOfOwC&pg=SA49-PA1&lpg=SA49-PA1&dq=Applied+Therapeutics.+Chapter+50,+Diabetes+Mellitus&source=bl&ots=zsbZOQnk5A&sig=oYnd1NmQqlTHy4XSmGEzjrLErFM&hl=en&sa=X&ei=0XQHT5T9GIXW0QHqhoDJAg&sqi=2&ved=0CCgQ6AEwAA#v=onepage&q=Applied%20Therapeutics.%20Chapter%2050%2C%20Diabetes%20Mellitus&f=false>

|  |  |  |
| --- | --- | --- |
| Characteristic | Type 1 Diabetes | Type 2 Diabetes |
| Former names | insulin-dependent or juvenile diabetes | non-insulin-dependent or adult-onset diabetes |
| % of Diabetic population | 5 – 10% | 90% |
| Age of onset |  |  |
| Rapidness of onset |  |  |
| Pancreatic function |  |  |
| Family history |  |  |
| Body weight |  |  |
| History of ketoacidosis |  |  |
| Clinical presentation | Moderate to severe symptoms which generally progress rapidly | Mild symptoms; often diagnosed on routine physical examination |

##### **Metabolic Syndrome**

**Metabolic syndrome** is a combination of [medical](http://en.wikipedia.org/wiki/Medicine) disorders that, when occurring together, increase the risk of developing [cardiovascular disease](http://en.wikipedia.org/wiki/Cardiovascular_disease) and [diabetes](http://en.wikipedia.org/wiki/Diabetes_mellitus)

Excessive caloric intake

Inherited genetic defect

Type 2 DM

Obesity

Insulin Resistance

Hyperinsulinemia

Hypertriglyceridemia

Hypercholesterolemia

↓ HDL

Atherosclerosis

HTN

**Atherosclerosis: Hardening of the arteries** occurs when fat, cholesterol, and other substances build up in the walls of **arteries** and form hard structures called plaques

**Miscellaneous:**

1. “Honeymoon Phase”

In a person who has type 1 diabetes, the insulin-producing beta cells in the pancreas are destroyed by immune cells. However, right after the time of diagnosis, some patients go through a "honeymoon phase" in which their existing beta cells still function. A number of [research projects](http://www.jdrf.org/index.cfm?page_id=101980) are currently taking place which hope to preserve the function of these existing beta cells after the honeymoon phase in people with T1D.

1. Somogyi Effect
   1. High morning blood glucose
   2. Normoglycemic at bedtime and a low blood glucose concentration at 3:00am
   3. Rebound hyperglycemia in the morning
   4. Secondary to an excessive increase in glucose production by the liver
      * Activated by insulin-counter regulatory hormones (cortisol, glucagon, epinephrine, and growth hormone)
2. Dawn Phenomenon
   1. High morning blood glucose
   2. Normoglycemic at bedtime and a normal or high blood glucose concentration at 3:00am
   3. Rebound hyperglycemia in the morning
   4. Secondary to circadian changes in insulin resistance

***THERAPY*** *– treatment*

***See details in Diabetes Therapeutics - lecture handout for drugs***

***See details in In-Patient Glycemic Control - slides for drugs***

**Hyperglycemic Crises**- Slides

Goals of treatment

* Stop ketogenesis (in DKA)
* Hydration: restore perfusion
* Decrease BG (< 200 mg/dl) and osmolality
* Correct electrolyte loss
* Avoid complications of treatment
* Identify and/or treat precipitation factors

Treatment

* Hydration
  + Goals: repletion of extracellular fluids
  + Assume 10% dehydration
  + Start 0.9% NaCl (Normal Saline) IV: usually 1 liter x 1hr
  + Followed by 4-14 ml/kg/h of NS or ½ NS until isovolemic
    - Calculate corrected Na
    - If Na high or normal ½ NS should be used
    - If Na low continue NS
  + Change NS to ½ NS + 5%Dextrose when BG 250 mg/dl in DKA or 300 mg/dl in HHS
  + Monitor hydration status and VS every hour
  + Duration of fluid replacement : 48 hrs
* Insulin
  + Needed to clear ketosis
  + Standard of care: IV
  + 100 units Regular insulin in 100 ml NS
  + Initial bolus: 0.1 units/kg
  + Followed by 0.1 units/kg/h
  + Reduced insulin infusion when BG reaches 250-300 mg/dl (0.05 to 0.1 units/kg/h)
  + Monitor BG q 1-2 hrs
  + Goal: decrease BG by 50-70 mg/dl/h
    - Double insulin infusion rate or decrease by half if goal not achieved
  + SQ insulin: Regular, lispro, and aspart can be used
    - Regular insulin: decrease in initial response
    - Hard to monitor in medical ward
* Electrolytes repletion
  + Potassium (nl: 3.5 - 5.0 mEq/L)
    - K > 5.3 mEq/L
    - K < 5.3 mEq/L
    - K < 3.3 mEq/L
      * Potassium chloride, acetate, or phosphate
  + Potassium infusion rate:
    - Peripheral line:
    - Central line:
  + Bicarbonate
    - Only administered if pH < 7.0
  + Phosphate
* Replace if level < 1.0 – 1.5 mg/dl

**In-Patient Glycemic Control -** Slides

Classification of hospital hyperglycemia

* *Medical history of diabetes*
* *Unrecognized diabetes*
* *Hospital related hyperglycemia*
  + *Medications*

Rationale for maintaining glycemic control

* Admission hyperglycemia has been associated with increase in morbidity and mortality
* Short term hyperglycemia affects
  + Immune function
  + Cardiovascular system
  + Thrombogenesis
  + Inflammatory markers
  + Endothelial cell function
  + Oxidative stress

*Target BG levels in the hospital (ADA) – The American Diabetes Association*

* Non critical care units
  + Preprandial: < 140 mg/dl (before meals or fasting blood glucose)
  + Postprandial: < 180 mg/dl (after meals blood glucose)
* Intensive care units
  + 140-180 mg/dl (NICE-SUGAR trial) - Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation

*Treatment options*

* Oral anti-hyperglycemic agents
* Subcutaneous insulin
  + Correction insulin
  + Schedule insulin
* Insulin infusion

**Oral antihyperglycemic agents**

* No efficacy data in hospitalized patients
* Hospitalized patients may present with contraindications to the use of oral agents:
  + NPO (nothing by mouth status)
  + Acute renal failure
  + Procedures that require dye
  + Heart failure exacerbations

*Example of Metformin vs iodinated contrast agents*:

According to the FDA-approved package insert, metformin use should be stopped at the time an iodinated contrast agent is administered, and the patient should wait 48 hours before resuming use of metformin.  It is not mandatory to do a repeat serum creatinine measurement before resuming metformin use, especially if the patient has normal renal function and no known comorbidities Metformin is a biguanide oral antihyperglycemic agent used to treat patients with non-insulin-dependent diabetes mellitius.   Metformin is contraindicated in patients that have compromised renal function.  Patients with compromised renal function will have elevated serum levels of metformin and are at risk of developing lactic acidosis.  Lactic acidosis can be fatal in about 50% of cases, but this condition only occurs at a rate of 0-0.084 cases per 1,000 patient years.  Because iodinated contrast agents are associated with nephrotoxicity, acute renal failure or a reduction in renal function caused by iodinated contrast media could potentially cause an accumulation of metformin and resultant lactate accumulation, hence the above recommendations for withholding metformin use for 48 hours following contrast administration.

**Correction SC insulin (Sliding scale)**

* Supplemental doses of short acting insulin given to treat hyperglycemia
  + 1-2 units of insulin will decrease BG ~ 50mg/dl
  + Can be used in addition to insulin and/or oral agents
  + Treats but does not prevent hyperglycemia
  + BG is usually checked 4 times/day and correction insulin is added if hyperglycemia
* Different doses (scales) of correction insulin are available depending on patient’s insulin resistance level
  + Modest, moderate or large doses
* All doses should start at 140 -150 mg/dL

Examples of correction insulin scale

|  |  |  |
| --- | --- | --- |
| Blood glucose (mg/dl) | Insulin dose (units) | Insulin dose (units) |
| 150-199 | 1 | 2 |
| 200-249 | 2 | 4 |
| 250-299 | 3 | 6 |
| 300-349 | 5 | 8 |
| 350-399 | 6 | 10 |
| > 400 | Call MD | Call MD |

* The use of correction insulin should be reflected on a schedule insulin dose
* Adding correction insulin to patients antihyperglycemic regimen:
  + Use 80% of TDD (total daily dose):
    - 50% basal, 50% prandial (if patient is eating)
  + Do not start prandial insulin if patient is not eating (NPO)

**Schedule SC Insulin**

* Schedule SQ insulin
  + Rapid or short acting
  + Intermediate
  + Long acting

**Insulin for Infusion**

* Only strategy developed for hospital use
* 100 units Regular insulin in 100 ml of 0.9% NaCl
* Indications:
  + Prolong fasting in type 1 DM
  + Critical illness
  + Perioperative time
  + Post organ transplant
  + DKA and HHS
  + Total parenteral nutrition
* Labor and delivery
* Advantages
  + Intensive insulin control
  + Greatest flexibility
* Disadvantages
  + Hourly monitoring
  + Risk of hypoglycemia

Insulin infusion protocol – Example

* Examples of protocols (TUH) – Temple University Hospital
* All protocols should contain
  + Threshold for starting the infusion
  + Target blood glucose range
  + Specific instructions on how to adjust the infusion rate
  + Specific instructions for conversion to SQ insulin
  + Treatment of hypoglycemia

Switching from an infusion to SQ

* Overlap for at least 2 hr
* Calculate SQ dose based on 80% of TDD
  + When patient insulin needs are stable for > 6hr
* If patient NPO use only basal insulin

*Issues with inpatient glucose control*

* A lot of variability:
  + Nutrition, medications, procedures
* Adjustment should be made daily
* Hospital formulary
* Complexity of some hospital protocols
* Variable health care professionals expertise
* Transition to outpatient (follow up)
* Fear of hypoglycemia

Complications – from slides

* Hypoglycemia
  + Most common in DKA (10-25% of pt)
  + Prevention: reduce insulin infusion rate and provide D5W when BG is 250 mg/dl
* Cerebral edema (~1% of children)
  + Associated with mortality rate of 40-90%
  + Prevention:
* Rebound DKA secondary to premature cessation of insulin
* Lactic acidosis secondary to dehydration, shock, infection or tissue hypoxia
* Thrombosis
  + DVT prophylaxis

***Deep vein thrombosis*** *(****DVT****) is the formation of a* [*blood clot*](http://en.wikipedia.org/wiki/Blood_clot) *("thrombus") in a* [*deep vein*](http://en.wikipedia.org/wiki/Deep_vein)*. Deep vein thrombosis commonly affects the* [*leg*](http://en.wikipedia.org/wiki/Leg) *veins (such as the* [*femoral vein*](http://en.wikipedia.org/wiki/Femoral_vein) *or the* [*popliteal vein*](http://en.wikipedia.org/wiki/Popliteal_vein)*) or the deep veins of the* [*pelvis*](http://en.wikipedia.org/wiki/Pelvis)*. Occasionally the veins of the* [*arm*](http://en.wikipedia.org/wiki/Arm) *are affected (such as in* [*Paget-Schrötter disease*](http://en.wikipedia.org/wiki/Paget-Schr%C3%B6tter_disease)*). A DVT can occur without* [*symptoms*](http://en.wikipedia.org/wiki/Symptoms)*, but in many cases the affected extremity will be* [*painful*](http://en.wikipedia.org/wiki/Pain)*,* [*swollen*](http://en.wikipedia.org/wiki/Swelling_(medical))*, red, and warm, and the* [*superficial veins*](http://en.wikipedia.org/wiki/Superficial_veins) *may be engorged.*

**Diabetes Complications** – from lecture handout

1. **Acute Complications**
2. Hypoglycemia
3. Can occur in all types of diabetes while taking insulin or certain oral hypoglycemic agents
4. Symptoms:
5. Hyperglycemia
6. Diabetic ketoacidosis (DKA)
7. Considered a true medical emergency
8. Develops when absolute insulin deficiency and excess contra-insulin hormones increase hepatic glucose production, decrease peripheral glucose utilization, and stimulate release of fatty acids from fat cells and production of ketone bodies by the liver
9. Hyperglycemic Hyperosmolar NonKetotic Syndrome (HHNK)
10. Considered a true medical emergency
11. Develops due to acute illness (Stroke, MI, Pneumonia), drugs, large glucose loads, dehydration
12. **Chronic Complications**
13. Macrovascular
14. Cardiovascular
15. Coronary Heart Disease
16. Most common cause of death
17. 7 X higher in women with Type 2 DM than in women without
18. Dyslipidemia (high blood cholesterol levels)
19. Hypertension
20. Cerebrovascular
21. 2-4 X higher risk of stroke
22. Associated risk factors include:
23. Peripheral Vascular Disease
24. Intermittent claudication occurs 5 X more often
25. Increases with age and duration of diabetes
26. Microvascular

* Neuropathy- affects up to 75% of diabetic patients

1. Peripheral neuropathy
2. Occur distally in either the hands or feet
3. Onset is insidious
4. Parathesia and pain
5. Diabetic foot ulcers are common
6. Leading cause of non-traumatic amputation in the United States
7. Autonomic neuropathy
8. Neurogenic bladder
9. Sexual dysfunction
10. Gastroparesis
11. Diabetic diarrhea

* Vision disorders

1. Retinopathy
2. Leading cause of blindness in the United States
3. Develops in 75 % of Type 1 DM patients after 15 years duration
4. DCCT:
5. Should get eye exam once a year
6. Cataracts/Glaucoma

* Renal

a- Responsible for 50 % of ESRD and most common reason to start dialysis

1. Hyperglycemia causes intraglomerular HTN and renal hyperperfusion
2. Nephropathy
3. Microalbuminuria: urinary albumin excretion > 30 mg / 24 h
4. Progresses to overt proteinuria ( > 500 mg / 24 h) and clinical nephropathy

Parathesia: a sensation of tingling, burning, pricking, or numbness of a person's skin with no apparent long-term physical effect. It is more generally known as the feeling of "pins and needles" or of a limb "falling asleep".

ESRD: End-stage renal disease, also known as [chronic kidney disease](http://en.wikipedia.org/wiki/Chronic_kidney_disease) (CKD), specifically the fifth stage of CKD - people who require dialysis or renal transplant.

HTN: hypertension

**Diabetes Therapeutics** – Lecture Handout

Standards of Medical Cares in Diabetes

Diab Care;Vol 34, Suppl 1, January 2011

<http://care.diabetesjournals.org/content/34/Supplement_1/S11.full.pdf+html>

<http://care.diabetesjournals.org/content/34/Supplement_1/S11.full#sec-15>

1. **Goals of Therapy:**
   * + 1. Strive for control at least equal to that achieved in the intensely treated patients in DCCT
       2. Maintain plasma glucose in an acceptable range throughout the day (70-130 mg / dl)
          1. Goal fasting glucose: 100 mg / dl

<http://www.healthypinoy.com/health/articles/diabetes/fasting-blood-sugar.html>

* + - 1. HgA1c: < 7 mg/dL (hemoglobin A1c test)
         1. A1c goals for selected individual patients is as close to normal (<6%) as possible without significant hypoglycemia

<http://depts.washington.edu/madclin/providers/guidelines/diabetes.html>

* + - 1. Keep patients free of symptoms
      2. Maintain normal growth and development in children
      3. Eliminate or minimize all other cardiovascular risk factors:
         1. Smoking - cessation
         2. Hypertension – blood pressure control
         3. Lipid profile - cholesterol management
         4. Weight management and physical activities

<http://circ.ahajournals.org/content/100/10/1134.full.pdf+html>

* + - 1. Decrease incidence of microvascular and macrovascular complications
      2. Educate the patient about disease state and its treatment

1. **Standards of Diabetes Care:**
   * + 1. Screening vs. Diagnostic testing

For many illnesses, there is a major distinction between screening and diagnostic testing. However, for diabetes, the same tests would be used for “screening” as for diagnosis. Diabetes may be identified anywhere along a spectrum of clinical scenarios ranging from a seemingly low risk individual who happens to have glucose testing, to a higher-risk individual whom the provider tests because of high suspicion of diabetes, to the symptomatic patient. The discussion herein is primarily framed as testing for diabetes in those without symptoms. Testing for diabetes will also detect individuals at increased future risk for diabetes, herein referred to as having prediabetes.

**Table 4**—Criteria for testing for diabetes in asymptomatic adult individuals

* + - 1. Initial medical work-up:
      2. Individualized management plan
      3. Routine medical visits for diabetes at least twice a year
      4. HgA1c every 3 – 6 months
      5. Foot exam at every diabetes visit
      6. Dilated eye exam every year
      7. Goal BP: systolic < 130 mmHg is appropriate for most patients with diabetes
      8. Goal Lipid Profile:

In individuals without overt CVD, the primary goal is an LDL cholesterol 100 mg/dl (2.6 mmol/l)

In individuals with overt CVD, a lower LDL cholesterol goal of\_70 mg/dl (1.8 mmol/l)

HDL cholesterol 40 mg/dl (1.0 mmol/l) in men and 50 mg/dl (1.3 mmol/l) in women, are desirable

Triglyceride levels \_150 mg/dl (1.7 mmol/l)

* + - 1. UA every year

1. **Non-Pharmacologic therapy:**
   1. Medical Nutrition Therapy
      * 1. Type 1 DM: Provide adequate calories to maintain growth
        2. Obese type2 DM: Calorie restrict 500-1000 kc below daily requirement
        3. Regularly schedules meals and snacks
        4. Specifics:
           1. Carbohydrates

90% of CHO intake enters the blood stream as glucose and is a major determinant of insulin secretion

Foods containing CHO from whole grains, fruits and vegetables should be included in a healthy diet

50 to 60% of total daily calories

* + - * 1. Sucrose

Does not increase hyperglycemia to a great extent

Patients with diabetes do not need to restrict sucrose-containing foods

They should be substituted for other CHO sources

* + - * 1. Artificial sweeteners

Saccharin and aspartame are acceptable in the dietary management of patients with diabetes

* + - * 1. Fat

< 7% of total daily calories from SATURATED FAT

< 200 mg cholesterol per day

* + - * 1. Alcohol

Daily intake should be limited to one drink for adult woman and 2 drinks for adult men

Alcohol should be consumed with food to prevent hypoglycemia

B. Exercise

1. Reduces cardiovascular risk factors

a. Lowers cholesterol

b. Lowers blood pressure

2. Augments weight-reduction diets

3. Increases utilization of glucose

4. Enhances insulin sensitivity

5. Reduces dose requirements or need for insulin or oral anti-diabetic agents

6. Recommendations:

a. Age > 35 needs exercise stress test

1. 30 minutes 3 to 4 times a week
2. Inspect feet daily before and after exercise

e. Wear proper footwear

1. **Pharmacologic Therapy**:
2. **Insulin**
   * + 1. Indications
          1. Monotherapy for Type 1 DM
          2. Monotherapy or in combination with other anti-diabetic agents for Type 2 DM
       2. Types of Insulin
          1. Beef (No Longer Available)
          2. Pork (No Longer Available)
          3. Human (recombinant DNA product)

|  |  |  |  |
| --- | --- | --- | --- |
| **Insulin Generic (Brand name)** | **How supplied** | **Manufacturer** | **Available** |
| Aspart Novolog® | 100 units/ml, 10 ml vial and  3 ml cartridge for pen | Novo Nordisk | Rx only |
| Lispro Humalog® | 100 units/ml, 10 ml vial and  3 ml cartridge for pen | Eli Lilly | Rx only |
| Glulisine Apidra® | 100 units/ml, 10 ml vial and  3 ml cartridge for pen | Aventis | Rx only |
| Regular Humulin R®  Novolin R® | 100 units/ml, 10 ml vial  **500 units/ml, 20 ml vial**  100 units/ml, 10 ml vial | Eli Lilly  **Eli Lilly**  Novo Nordisk | OTC  **Rx only**  OTC |
| NPH Humulin N®  Novolin N® | 100 units/ml, 10 ml vial  100 units/ml, 10 ml vial | Eli Lilly  Novo Nordisk | OTC  OTC |
| Glargine Lantus® | 100 units/ml, 10 ml vial and  3ml cartridge for pen | Aventis | Rx only |
| Detemir Levemir® | 100 units/ml, 10 ml vial and  3ml cartridge for pen | Novo Nordisk | Rx only |
| **Combination Products** |  |  |  |
| Insulin Humulin 70/30®  70% NPH Novolin 70/30®  30% R | 100 units/ml, 10 ml vial and  3ml cartridge for pen | Eli Lilly  Novo Nordisk | OTC |
| Insulin Humulin 50/50®  50% NPH  50% R | 100 units/ml, 10 ml vial and  3ml cartridge for pen | Eli Lilly | OTC |
| Insulin Humalog 70/30®  70% NPH-like  30% lispro | 100 units/ml, 10 ml vial and  3ml cartridge for pen | Eli Lilly | Rx only |
| Insulin Novolog 75/25®  75% NPH-like  25% aspart | 100 units/ml, 10 ml vial and  3ml cartridge for pen | Novo Nordisk | Rx only |

**NPH insulin** (or neutral protamine Hagedorn) (also known as Humulin N, Novolin N, Novolin NPH, NPH Lletin II, and isophane insulin), is an intermediate-acting insulin. This is a suspension of crystalline zinc insulin combined with the positively charged polypeptide, [protamine](http://en.wikipedia.org/wiki/Protamine). When injected subcutaneously, it has an intermediate duration of action, meaning longer than that of regular insulin, and shorter than [ultralente](http://en.wikipedia.org/w/index.php?title=Ultralente&action=edit&redlink=1), [glargine](http://en.wikipedia.org/wiki/Insulin_glargine) or [detemir](http://en.wikipedia.org/wiki/Insulin_detemir).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Type of Insulin** | **Onset (hours)** | **Peak (hours)** | **Duration (hours)** | **Appearance** |
| Rapid-acting Aspart  Lispro  Glulisine | < ¼  < ¼  < ¼ | 1-3  1-3  1-2 | 2-4  2-4  2-4 |  |
| INHALED INSULIN (removed) | ½ - 1 | 2-4 | 4-6 |  |
| Short-acting Regular | ½ - 1 | 2-4 | 4-6 |  |
| Intermediate-acting Lente (removed)  NPH | 1-2  1-2 | 6-14  6-14 | 12-18  16-24 |  |
| Long-acting Glargine  Detemir  Ultralente (removed) | 1-2  1-2  4-10 | 2-20 (peakless)  2  8-30 | 20-24+  24+  18-36+ |  |

Adapted from AphA: Special report: New Approaches to Insulin Therapy

**Idealized Profiles of Human Insulin and Insulin Analogs**

**0**

**24 hours**

**Plasma Insulin**

**Regular**

**NPH**

**Detemir**

**Time**

**Glargine**

**Aspart, Glulisine, Lispro**

Rosenstock J. Goldstein BJ et al, eds. *Textbook of Type 2 Diabetes*. Martin Dunitz;2003:131-154.

Plank J et al. *Diabetes Care*. 2005;28:1107-1112.

* + - 1. Pharmacokinetics
         1. Absorption

After subcutaneous injection, directly into blood stream

Highly irregular, interpatient variability

* + - * 1. Excretion

30-80% is cleared by the kidneys

* + - 1. Mixing Insulins

|  |  |
| --- | --- |
| Type of Insulin | Compatible Insulins |
| Aspart  Lispro  Glulisine Regular NPH  Glargine  Detemir | NPH  NPH  NPH  NPH  Aspart  Lispro  Glulisine  Regular  **NONE**  **NONE** |

* + - 1. Frequency of shots
         1. Patient dependent
         2. Type 1 DM

Multiple injections daily to mimic normal insulin release in non-diabetics

* + - * 1. Type 2 DM

Generally used with oral agents

Initially, one dose per day may be sufficient (plus oral agents)

2 or more injections frequently needed as disease progresses

* + - 1. Intensive Insulin Therapy
         1. Insulin pumps

Battery operated pump and computer

* + - * 1. Multiple daily injections
        2. Components of intensive insulin therapy

Multicomponent insulin regimen

Balance of food intake, exercise and insulin dosage

Multiple daily self-monitoring of blood glucose levels

Patient self adjustment of food intake and insulin dosage

Individualized target blood glucose and HgA1c levels

Frequent contact between patient and diabetes team

Intensive patient education

Psychological support

* + - * 1. DCCT: (Diabetes Control and Complications Trial)

1141 patient followed for 7 years

Hypothesis: Does tight glucose control prevent or limit the progression of diabetes complications - Describe the results of DCCT trial.

<http://general-medicine.jwatch.org/cgi/content/full/1995/1110/1>

the trial showed that tight glycemic control with intensive therapy can reduce microvascular complications (see Journal Watch accession number 931005001 and N Engl J Med 1993; 329:977).

* + - 1. Usual total daily dose of insulin

|  |  |  |
| --- | --- | --- |
| **Diabetes Type** | **Situation** | **Dose (Unit/kg) (actual body weight)** |
| Type 1  Type 1  Type 1  Type 2 | Initial dose  Honeymoon phase  With Ketosis: during illness  See below | 0.5-0.6  0.1-0.4  0.5-1.0  See below |

**Algorithm to add Once-Daily Insulin to patients with Type 2 diabetes**

* Start with **10 units** of a long or intermediate-acting insulin at bedtime
  + Glargine
  + Detemir
  + NPH
* Adjust according to algorithm

**Mean self-monitored FPG values from preceding 2 days Increase of insulin dosage (units per day)**

> 180 mg/dl 8

140-180 6

120-140 4

100-120 2

* + - 1. Factors altering onset and duration of insulin action

|  |  |
| --- | --- |
| Factor | Comments |
| Route of administration | Onset of action rapid and duration shorter for IV>IM>SQ |
| Factors altering clearance Renal function  Insulin Antibodies  Thyroid function | Renal failure decreases insulin clearance  IgG antibodies bind to insulin as it is absorbed and release it slowly  Hyperthyroid increases clearance, but also increases insulin action |
| Factors altering SQ absorption   Site of injection  Exercise of injected area  Ambient temperature  Local Massage  Smoking  Lipohypertrophy | Factors that increase blood flow increase absorption of regular insulin  Fastest from abdomen, intermediate from the arm, and slowest from the thigh  Within 1 hours can increase absorption rate  Heat increases absorption rate  Increases absorption rate  Vasoconstriction may decrease absorption rate  Absorption delayed |

* + - 1. Adverse effects
         1. Hypoglycemia
         2. Weight gain
         3. Insulin-induced hyperglycemia (“Somogyi effect”)
         4. Insulin antagonism/resistance
         5. Rapid insulin metabolism
         6. Local reactions to the “foreign” proteins

<http://www.aafp.org/afp/2004/0801/p489.html>

http://www.elephantcare.org/Drugs/insulin.htm

**Describe the course of action if a patient finds his/her BS < 50 mg /dl**

<http://books.google.com/books?id=_WUxJRAioBYC&pg=PA263&lpg=PA263&dq=course+of+action+of+diabetes+with+blood+sugar+%3C+50+mg+/dl&source=bl&ots=6EMXJvnBjM&sig=MOjTo0YD8ef9ZQpLOFOnSHH0NUM&hl=en&sa=X&ei=6jELT_65Nabh0QHxwr3wDA&ved=0CFEQ6AEwBA#v=onepage&q=course%20of%20action%20of%20diabetes%20with%20blood%20sugar%20%3C%2050%20mg%20%2Fdl&f=false>

Once hypoglycemia is verified, patients hwo are able to eat or drink should be given 15g of carbohydrate (glucose tablets, orange juice, ect.). Consider using 30g of carbohydrate if the glucose is < 50 mg/dL (2.8 mmol/L). Monitor the blood glucose every 15-30 minutes until levels are stabilized (blood glucose <100 mg/dL or 5.6 mmol/L). If the patient is unconscious or unable to eat or drink because of severe neuroglycopenia, two treatment options are available. The most common treatment- especially in the hospital and emergency room setting – is IV glucose. Administer a bolus of 10-20 ml of 50% dextrose (glucose) followed by 10% dextrose infused at 100 ml/hr until blood glucose levels are stabilized. Document the blood glucose levels every 30 minutes during initial IV treatment. The second treatment option is the SC or IM administration of glucagon. Glucagon is not the preferred agent for the treatment of hypoglycemia in most hospital settings, but it may be the only option in some individuals – for logistical reasons or special circumstances. The standard dose is 1.0 mg for adults and 0.5 mg for children weighing less than 50 pounds (22.5 kg)

* + - 1. Sick Day management
         1. Continue taking your basic dose of insulin even if you are not eating well or have nausea and vomiting
         2. Test your blood glucose more frequently (every 3-4 hours)
         3. If indicated, give supplemental doses of insulin
         4. Begin testing urine for ketones
         5. Drink plenty of fluid and maintain adequate caloric intake
         6. Call MD if BG > 300 mg/dl or persistent ketones in urine

##### **Commonly Used Insulin Regimens** (Adapted from AphA: Special Report)

<http://tmedweb.tulane.edu/pharmwiki/doku.php/insulin_regimens>

*Endogenous Insulin secretion in healthy individuals*

KEY

B = Breakfast

L = Lunch

D = Dinner

HS = Bedtime

= Rapid acting or Short acting

= Intermediate acting

= Glargine / Detemir

##### B L D HS B

*Twice daily regimen*

##### B L D HS B

##### *Three times daily regimen*

B L D HS B

*Four times daily regimen*

##### B L D HS B

##### *Four times daily regimen*

B L D HS B

##### **Site of Action of Oral Anti-diabetic Medications**

Liver

###### Reduced hepatic glucose production

Pancreas Periphery

Increase secretion of insulin Increased uptake of glucose

GI Tract

###### Delay absorption of dietary carbohydrates

**SUMMARY SLIDES FOR DRUG SELECTIONS**

<http://www.slideshare.net/7260678/thiazolidinediones-8-presentation>

* 1. **Sulfonylureas**

1. Indications

a. Monotherapy or in combination with other anti-diabetic agents for Type 2 DM

2. Mechanism of action

a. Initially increase insulin levels

i. Increase B-cell secretion of insulin in the pancreas

3. Patient selection - Which type of patient is most suitable for sulfonylurea therapy? – **CASE STUDIES**

* Type 2 diabetes without dyslipidemia
* Normal weight
* Hyperglycemia despite following meal planning and an exercise program
* Ability and willingness to follow a reasonable dietary program
* Hyperglycemia for less than 5 years
* Age older than 30 years

<http://www.netce.com/coursecontent.php?courseid=686>

4. Efficacy

a. All equally effective

b. 54-72 mg/ dl fall in FPG (fasting plasma glucose); 1.5-2.0 % decrease in HgA1c

<http://books.google.com/books?id=56D5wArcMLgC&pg=PA548&lpg=PA548&dq=efficacy+of+sulfonylureas+mg/dL+fall+in+FPG&source=bl&ots=y-Wufc_ARh&sig=IcSbSWToj8ykH4wKLxPd_21UoC8&hl=en&sa=X&ei=kk8LT6CoBcKF0QHg-IX1Dg&sqi=2&ved=0CFMQ6AEwCA#v=onepage&q=efficacy%20of%20sulfonylureas%20mg%2FdL%20fall%20in%20FPG&f=false>

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5. Response rate – 60-70%

a. Primary failure

i. Does not respond initially

b. Secondary failure

i. 10% of patients per year

ii. Failure to follow diet

iii. Stressful condition

iv. Worsening of disease

6. Administration

a. 30 minutes before a meal

7. Adverse Effects - Name 5 adverse effects of sulfonylureas.

* Hypoglycemia (most significant adverse effect)
* Digestive manifestations (nausea, epigastric pain, liver pain)
* Haematological manifestations (pancytopenia, autoimmune hemolytic anemia, thrombocytopenia)
* Weight gain
* Disulfiram-type reaction if combined with alcohol

<http://books.google.com/books?id=fiAclxvKblkC&pg=PA82&lpg=PA82&dq=adverse+effects+of+sulfonylureas&source=bl&ots=ece9NYYSKt&sig=c-LzdYJnLxr7JhvMJ2GvLrQayqs&hl=en&sa=X&ei=8VMLT5KwGYnX0QH3iaioAg&sqi=2&ved=0CEYQ6AEwBQ#v=onepage&q=adverse%20effects%20of%20sulfonylureas&f=false>

<http://www.doctortipster.com/3970-oral-antidiabetic-medication-classes-mechanism-of-action-and-side-effects.html>

8. Monitoring parameters

a. BS, renal function, HgA1c every 3-6 months

b. Signs and symptoms of adverse effects

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Drug**  (Brand Name) Available tablet strengths (mg) | **Typical dosing regimen** | **Usual Dose** | **Mean Half-Life** | **Duration of Action** |
| **First Generation** | |  |  |  |
| Acetohexamide  (Dymelor®)  250, 500 mg | 250 or 500 mg daily, ↑ by 250 mg daily every 1-2 weeks | 250 – 1500 mg daily or divided BID | 5 hours | 12 – 18 hours |
| Chlorpropamide  (Diabinese®)  100, 250 mg | 100 or 250 mg daily, ↑ by 100 or 250 mg every 1-2 weeks | 100 – 500 mg daily |  |  |
| Tolazamide  (Tolinase®)  100m 250, 500 mg | 100 – 250 mg daily, ↑ by 100 or 250 mg every 1-2 weeks | 200 – 1000 mg daily or divided BID | 7 hours | 12 – 24 hours |
| Tolbutamide  (Orinase®)  250, 500 mg | 250 mg BID, ↑ by 250 mg daily every 1-2 weeks | 500 – 3000mg divided BID or TID | 7 hours | 6 – 12 hours |
| **Second Generation** | |  |  |  |
| Glimepiride  (Amaryl®)  1, 2, 4 mg | 1-2 mg daily | 1 – 8 mg daily | 9 hours | 24 hours |
| Glipizide  (Glucotrol®)  5, 10 mg | 2.5-5 mg daily,  ↑ by 2.5 or 5 mg every 1-2 weeks | 2.5 – 40 mg daily or divided BID | 2-4 hours | 12-24 hours |
| Glipizide extended-release  (Glucotrol XL®)  5, 10 mg | 5 mg daily, ↑ by 5 mg every 1-2 weeks | 5-20 mg daily | 4-13 hours | 24 hours |
| Glyburide  (Diabeta®, Micronase®)  1.25, 2.5, 5 mg |  |  | 4-13 hours | 12-24 hours |
| Micronized Glyburide  (Glynase®)  1.5, 3 mg | 1.5 mg daily, ↑ by 1.25 mg every 1-2 weeks | 1-12 mg daily | 4 hours | 24 hours |

What are some commonly prescribed combination oral medications for diabetes?

<http://www.slideshare.net/7260678/thiazolidinediones-8-presentation>

* 1. **Biguanide**

1. Metformin (Glucophage®)

|  |  |  |  |
| --- | --- | --- | --- |
| **(Brand name)** | **How supplied** | **Dosing** | **Manufacturer** |
| Glucophage®  Glucophage XR® | 500 mg  850 mg  1000 mg  XR 500 mg  XR 750 mg | Initial:  500 mg BID  Maintenance:  1500 mg per day  Maximum:  2550 mg per day | Bristol Meyers Squibb |

2. Indication

a. Monotherapy or in combination with other anti-diabetic agents for Type 2 DM

3. Mechanism of action

a. Decrease hepatic glucose output

b. Enhances peripheral muscle glucose uptake

c. Does not affect insulin secretion

<http://www.uptodate.com/contents/metformin-in-the-treatment-of-diabetes-mellitus>

4. Patient selection

a. UKPDS-34 - Explain the clinical relevance of UKPDS-34.

<http://www.rxfiles.ca/rxfiles/uploads/documents/diabetes-metformin-lacticacidosis-qanda.pdf>

The benefit of metformin in reducing mortality and macrovascular complications in obese patients with Type 2 diabetes (T2DM) was established in the UKDPS-34 trial

<http://www.bmj.com/content/343/bmj.d4169?tab=responses>

Effect of Intensive blood-glucose control with metformin on complications in overweight  
patients with type 2 diabetes (UKPDS 34). Lancet 1998;352:854-65

5. Response rate – 80-90%

6. Efficacy

a. 19-84 mg / dl fall in FPG; 0.6-2.0% decline in HgA1c

<http://books.google.com/books?id=YPqUPj8cIjEC&pg=PA293&lpg=PA293&dq=efficacy+of+metformin+mg/dl+fall+in+FPG+%25+decline+in+HgA1c&source=bl&ots=fACH4yORes&sig=AqOxmTO_i3ECqj0EyXW6iN4ma7Y&hl=en&sa=X&ei=sXoLT9r4NYj30gGy9aDxBQ&sqi=2&ved=0CDMQ6AEwAw#v=onepage&q=efficacy%20of%20metformin%20mg%2Fdl%20fall%20in%20FPG%20%25%20decline%20in%20HgA1c&f=false>

pp 293

b. Patients with higher baseline FPG will achieve greater reductions

7. Contraindications - Name the contraindications for using metformin

* Warning:
  + Lactic acidosis
* Contraindications:
  + Renal disease or renal dysfunction
  + Acute or chronic metabolic acidosis
  + Known hypersensitivity to metformin HCl
  + IV administration of radiologic iodinated contrast material

8. Adverse effects

a. GI (30%)

b. Lactic acidosis

9. Advantages

a. Effect on lipid profile

c. Does not cause hypoglycemia when used as monotherapy

10. Monitoring parameters

a. Baseline renal function, LFT, and annually thereafter

b. Glycemic control

c. HgA1c every 3-6 months

**D. Thiazolidinediones**

1. Troglitazone (Rezulin®) first in the class approved in 1997; withdrawn from market

**Black Box Warning**

Thiazolidinediones, cause or exacerbate congestive heart failure in some patients. After initiation, and after dose increases, observe patients carefully for signs and symptoms of heart failure.

If these signs and symptoms develop, discontinuation or dose reduction must be considered.

Not recommended in patients with symptomatic heart failure. Use in patients with NYHA Class III or IV heart failure is contraindicated.

1. Pioglitazone (Actos®)
2. Rosiglitazone (Avandia®)

|  |  |  |  |
| --- | --- | --- | --- |
| **(Brand name)** | **How supplied** | **Dosing** | **Manufacturer** |
| Pioglitazone  Actos®  Rosiglitazone  Avandia® | 15 mg  30 mg  45 mg  2 mg  4 mg  8 mg | Initial:  15 mg daily  Maintenance:  30 mg to 45 mg daily  Maximum:  45 mg daily  Initial:  4 mg daily  Maintenance:  4 mg to 8 mg daily  Maximum:  8 mg daily | Takeda  GlaxoSmithKline |

Describe the results of the recent meta-analysis regarding rosiglitazone (Avandia®) - Avandia (Now ONLY through restricted access program)

<http://www.nejm.org/doi/full/10.1056/NEJMoa072761>

<http://www.medpagetoday.com/Endocrinology/Diabetes/5701>

CLEVELAND, May 21 -- A meta-analysis of data from 42 clinical trials found a 43% increase in relative risk of myocardial infarction among type 2 diabetics treated with rosiglitazone (Avandia).

3. Indications: (Type 2 DM Only)

a. Pioglitazone: Monotherapy or in combination with sulfonylureas, metformin, or insulin

b. Rosiglitazone: Monotherapy or in combination with sulfonylureas, metformin **(NOT WITH INSULIN**)

4. Mechanism of action

a. Bind to newly discovered class of nuclear receptors, peroxisome proliferator-activated receptor-gama (PPAR-gama)

b. In adipose tissue, muscle tissue and the liver

c. Enhances insulin sensitivity

5. Patient selection

a. Insulin sensitizing agents

b. Patients who have failed/contraindicated to other agents

6. Response rate- 50-60%

7. Efficacy

a. 25-50 mg / dl fall in FPG; 0.5-1.5% decline in HgA1c

8. Contraindications

a. Pregnancy

b. Significant liver disease

c. Cardiac failure

<http://www.healthhype.com/thiazolidinediones-for-diabetes-actions-side-effects.html#contraindications-of-thiazolidinediones>

9. Drug interactions

a. Cholestyramine

b. Oral contraceptives

10. Adverse effects

a. Hepatic (liver failure/death); primarily seen with Troglitazone

b. GI

c. Hematologic

d. Edema

e. Changes in bone density

11. Advantages

a. Can lower insulin requirements

b. Does not cause hypoglycemia when used as monotherapy

c. Does not cause hyperinsulinemia

d. Effects on lipids

i. Pioglitazone:

ii. Rosiglitazone

12. Disadvantages

a. Cost

b. Weight gain

c. Takes up to 12 weeks to see a maximum response

13. Monitoring parameters

a. LFT baseline then periodically

b. Glycemic control

c. HgA1c every 3-6 months

* + - 1. **Alpha-glucosidase inhibitors**

Acarbose (Precose®)

Miglitol (Glyset®)

|  |  |  |  |
| --- | --- | --- | --- |
| **(Brand name)** | **How supplied** | **Dosing** | **Manufacturer** |
| Acarbose  Precose®  Miglitol  Glyset® | 25 mg  50 mg  100 mg  25 mg  50 mg  100 mg | Initial:  25 mg TID (with first bite of each meal)  Maintenance:  50 mg TID (if < 60 kg)  100 mg TID (if > 60 kg)  Maximum:  100 mg TID  25 mg TID (with first bite of each meal)  Maintenance:  50 mg to 100 mg TID  Maximum:  100 mg TID | Bayer  Pfizer |

2. Indications

a. Monotherapy or in combination with other anti-diabetic agents for Type 2 DM

3. Mechanism of action

a. Glucosidase inhibitors are competitive, reversible inhibitors of pancreatic a-amylase and membrane-bound intestinal a-glucosidase hydrolase enzymes.  Use of these drugs leads to blocking the enzymatic degradation of complex carbohydrates in the small intestine.  Thus, less carbohydrate is absorbed and the carbohydrate that is absorbed is delayed

<http://www.rushakoff.com/inpatient%20diabetes%20course/Oral%20agents/alpha/1.htm>

b. Delays breakdown of ingested complex carbohydrates into glucose; decreases absorption

c. Reduces postprandial hyperglycemia

4. Drug interactions

a. Digestive enzymes

b. Intestinal absorbents

5. Efficacy

a. 35-40 mg / dl fall in FPG and 60-70 mg / dl fall in postprandial glucose

b. 0.7-1.0 % decline in HgA1c

<http://www.jfponline.com/pages.asp?AID=8629>

Postprandial glucose – The alpha-glucosidase inhibitors are effective in lowering PPG because they delay carbohydrate absorption

6. Adverse effects

a. Primarily in GI tract nature (flatulence, diarrhea and abdominal distention) – These effects occur because the delay in carbohydrate absorption increases fermentation and formation of intestinal gases

<http://books.google.com/books?id=5zd_W_PUwvYC&pg=PA1077&dq=alpha-glucosidase+inhibitors+adverse+effects&hl=en&sa=X&ei=VI8LT_i3F6Lv0gHv9rDiBQ&ved=0CFQQ6AEwBQ#v=onepage&q=alpha-glucosidase%20inhibitors%20adverse%20effects&f=false>

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7. Contraindications

a. Active obstructive or inflammatory bowel disease and ulceration of colon

b. Contraindicated in patients with chronic liver diseases and substantial renal impairment (serum creatinine > 2 mg/dL)

<http://books.google.com/books?id=5zd_W_PUwvYC&pg=PA1077&dq=alpha-glucosidase+inhibitors+adverse+effects&hl=en&sa=X&ei=VI8LT_i3F6Lv0gHv9rDiBQ&ved=0CFQQ6AEwBQ#v=onepage&q=alpha-glucosidase%20inhibitors%20adverse%20effects&f=false>

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8. Advantages

a. Does not cause hypoglycemia

b. Does not cause hyperinsulinemia

9. Disadvantages

a. Less effective than other agents

b. GI side effects

10. Monitoring parameters

a. Baseline LFT’s, every 3 months during the first year and periodically thereafter

b. Glycemic control

c. HgA1c every 3 –6 months

* + - 1. **Meglitinides**

Repaglinide (Prandin®)

Nateglinide (Starlix®)

|  |  |  |  |
| --- | --- | --- | --- |
| **(Brand name)** | **How supplied** | **Dosing** | **Manufacturer** |
| Repaglinide  Prandin®  Nateglinide  Starlix® | 0.5 mg  1 mg  2 mg  60 mg  120 mg | Initial:  0.5 mg (within 15 minutes of each meal) if hypoglycemic agent naïve patient or patients with HgA1c < 8%  Or  1-2 mg (within 15 minutes of each meal) if HgA1c > 8%  Maintenance:  0.5 mg to 4 mg (within 15 minutes of each meal  Maximum:  16 mg daily  Initial:  60 mg (within 15 minutes of each meal)  Maintenance:  60 mg to 120 mg (within 15 minutes of each meal  Maximum:  360 mg daily | Novo Nordisk  Novartis |

2. Indications

a. Monotherapy or in combination with metformin for Type 2 DM

b. Structurally not a sulfonylurea

3. Mechanism of action

a. Similar to sulfonylureas

b. Increases B-cell secretion of insulin

c. Enhance effect of endogenous insulin at receptor site

4. Efficacy

a. 65-75 mg / dl fall in FPG; 05-2.0 % decline in HgA1c

5. Adverse effects

a. Hypoglycemia

b. Headache

6. Caution

a. Liver dysfunction

7. Advantages

a. Short acting

b. Slightly less hypoglycemia then sulfonylureas

8. Monitoring

a. Glycemic control

b. HgA1c every 3-6 months

* + - 1. **Amylin Analogue**

Pramlintide (Symlin®)

Indications

Type 1 DM as an adjunct to treatment with mealtime insulin therapy

Type 2 DM as an adjunct to treatment with mealtime insulin therapy

Mechanism of action - Amylinomimetic

Modulates gastric emptying

Prevention of postprandial rise in glucagon output

Increased satiety, leading to decreased caloric intake and weight loss

3. Administration

60 mcg SQ immediately prior to a meal, increase to 120 mcg in 3-7 days if no severe nausea

Decrease pre-prandial insulin dose by 50%

4. Adverse effects

a. Hypoglycemia

b. Nausea

5. Caution

a. increased risk of hypoglycemia

* + - 1. **Incretin Analogue**

Exenatide (Byetta®)

Liraglutide (Victoza®)

|  |  |  |  |
| --- | --- | --- | --- |
| **(Brand name)** | **How supplied** | **Dosing** | **Manufacturer** |
| Exenatide  Byetta®  Liraglutide  Victoza® | 5 mcg  10 mcg  0.6 mg  1.2 mg  1.8 mg | Initial:  5 mcg SQ BID  Maintenance:  10 mcg SQ BID  Initial:  0.6 mg SQ daily  Maintenance:  1.2 mcg SQ daily  Maximum  1.8 mg SQ daily | Amylin  NovoNordisk |

1. Indications

a. Type 2 DM as an adjunct to treatment with metformin, sulfonylurea or both.

2. Mechanism of action

a. GLP-1 (Glucagon-like-Peptide-1)

i. Stimulates insulin release from pancreas in presence of hyperglycemia

ii. Prevention of postprandial rise in glucagon output

iii. Increased satiety, leading to decreased caloric intake and weight loss

3. Adverse effects

a. Hypoglycemia (minimal)

b. Nausea

c. Pancreatitis

4. Caution

a. Exenatide: Avoid in patient with severe renal impairment (CrCl , 30 ml/min)

b. Liraglutide: No Dosage adjustment needed in renal impairment

* + - 1. **DPP-IV Inhibitor**

Sitagliptin (Januvia®)

Saxagliptin (Onglyza®)

|  |  |  |  |
| --- | --- | --- | --- |
| **(Brand name)** | **How supplied** | **Dosing** | **Manufacturer** |
| Sitagliptin  Januvia®  Saxagliptin  Onglyza® | 25 mg  50 mg  100 mg  2.5 mg  5 mg | Initial:  100 mg po daily  Initial:  5 mg po daily | Merck  BMS |

1. Indications

a. Type 2 DM as monotherapy or as an adjunct to treatment with metformin, or thiazolidinediones

2. Mechanism of action

a. Inhibits DPP-IV enzyme thereby increasing concentrations of active GLP-1

i. Stimulates insulin release from pancreas in presence of hyperglycemia

ii. Prevention of postprandial rise in glucagon output

iii. Increased satiety, leading to decreased caloric intake and weight loss

3. Adverse effects

a. Hypoglycemia (minimal)

b. Nausea

c. Diarrhea

4. Caution

a. Sitagliptin: Dose adjust with renal insufficiency

i. . CrCl 30 to 50 ml/min : 50 mg po once daily

ii. CrCl < 30 ml/min : 25 mg po once daily

b. Saxagliptin: Dose adjust with renal insufficiency

i: CrCl < 50 ml/min: 2.5 mg po once daily

**Algorithm for Management of Type 2 Diabetes Mellitus**

(Adapted from Diabetes Care, Vol 32, No. 1, Jan 2009: 193-203)

**Standards of Medical Care in Diabetes- 2011 (Summary)**

|  |  |
| --- | --- |
| **Topic** | **Action** |
| **Prevention / Delay of Type 2 DM** | Patients with IFG or IGT should be counseled on weight loss of 5-10 % of body weight as well as increasing physical activity to ~ 150 minutes per week.  In addition to lifestyle modifications, metformin may be considered in those who are at very high risk. |
| **Immunizations** | Annually provide an influenza vaccine to all diabetic patients > 6 months of age.  Provide at least one lifetime pneumococcal vaccine for adults with diabetes. |
| **Blood pressure** | Goal: < 130/ < 80.  Pharmacologic therapy for patients with hypertension and diabetes should be with a regimen of either an ACEi or ARB. |
| **Dyslipidemia** | Goal: < 100 mg/dl (< 70 mg /dl)  Alternate Goal: Reduction in LDL 30-40% from baseline  Statins should be added to lifestyle modifications, regardless of baseline lipids, for diabetic patients with overt CVD or are over 40 years of age with risk factors. |
| **Antiplatelets** | Use Aspirin therapy 75-162 mg per day for diabetic patients as:  Primary prevention for patients at high risk  (10-year risk > 10%):   * + - Men > 50 years of age     - Women > 60   Secondary prevention for patients with a history of CVD. |
| **Smoking cessation** | Advise all patients not to smoke. |