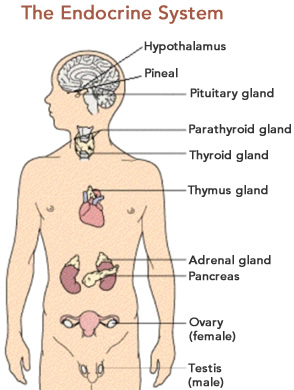
**Pharmacology of the Endocrine System**

* Pituitary and hypothalamic hormones
* Thyroid and antithyroid Drugs
* Adrenal Drugs
* Pancreatic Drugs
* Gonadal hormones and inhibitors



**Endocrine glands all over the body**

**Hormone**

* A substance that released in one tissue and travels through the circulation (usually) to the target tissue.
* Hormones reach all parts of the body, but only target cells are equipped to respond

**Endocrine Functions:** 1- Maintain Internal Homeostasis

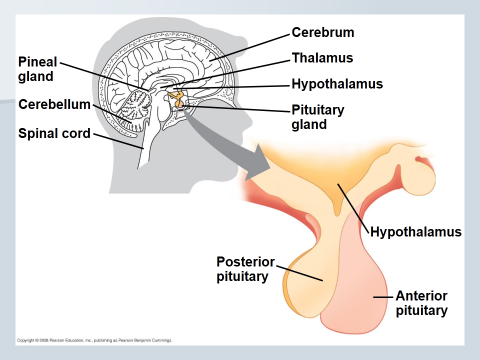
2- Support Cell Growth

3- Coordinate Development

4- Coordinate Reproduction and fertility

5- Facilitate Responses to External Stimuli

**Hypothalamic & Pituitary Hormones:**

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**The position of pituitary gland and hypothalamus in the brain**

**The Pituitary Gland**

Anterior pituitary gland makes and releases Hormones under regulation of hypothalamus:

1- Growth Hormone (GH)

2- Thyroid-stimulating Hormone (TSH)

3- Adrenocorticotropin (ACTH)

4- Follicle-stimulating Hormone (FSH)

5- Leutinizing Hormone (LH)

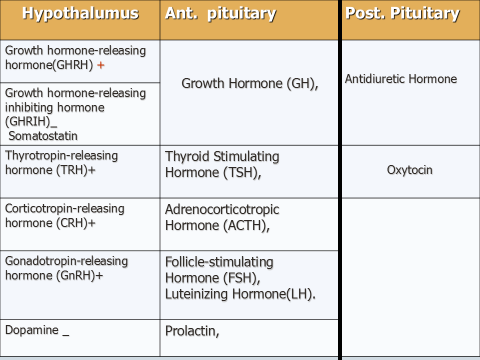
6- Prolactin

The posterior pituitary stores and secretes hormones that made in hypothalamus:

1- Oxytocin

2- Antidiuretic hormone (ADH)

**Hormones released from hypothalamus and both lobes of pituitary glands**



**Hypothalamic hormones:**

**1- Growth Hormone- Releasing Hormone (GHRH):**

Together with somatostatin controls release of the GH from the anterior pituitary.

* Diagnostic uses of GHRH: To test pituitary function in patients with GH deficiency.
* Therapeutic uses of GHRH: To enhance GH secretion.

**2- Somatostatin (Growth hormone-releasing inhibiting hormone (GHRIH) :**

* Inhibits GH release and TSH from the anterior pituitary.
* Inhibits release of most GI hormones, reduces gastric acids and pancreatic secretion. (glucagon, insulin & gastrin)

**Clinical uses of Somatostatin:**

- Somatostatin is of no clinical value because of its short half-life (<3 min)

**- Octreotide**, a synthetic somatostatin analogue with a longer duration of action.

**3- Thyrotropin-Releasing Hormone (TRH):** Stimulates release of thyrotropin (TSH), used in diagnostic testing of thyroid dysfunction.

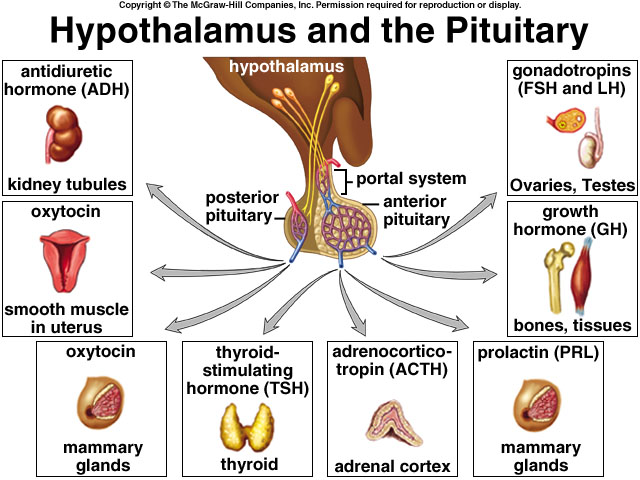
**4- Corticotropin Releasing Hormone (CRH)**

It stimulates secretion of ACTH.

**5- Gonadotropin-Releasing Hormone (GnRH):** Stimulate the gonadotrophic cell to produce and release LH and FSH.

**6- Prolactin-Inhibiting Hormone (PIH, dopamine):**

Dopamine is the physiologic inhibitor of prolactin release.



**Pituitary Hormones**

**Anterior pituitary Hormones**

**Growth Hormone**

**Growth Hormone Activity**

1. Increases plasma free fatty acids (source of energy for muscle tissue)
2. Increases hepatic glucose output
3. Decreases insulin sensitivity in muscle
4. Is protein anabolic hormone

**Growth Hormone Deficiency**

* In childhood: short stature and hypoglycemia.
* Adults: generalized obesity, reduced muscle mass.

**Growth Hormone Excess** (Mainly due to benign pituitary tumor)

* In adults causes **acromegaly**
* If this occurred before the long bone epiphyses close, it leads to the rare condition, **gigantism.**



**Growth Hormone Excess**

**Treatment of excess GH disorders:**

1- Synthetic Somatostatin (Octreotide)

2- Dopamine agonists (Bromocriptine)

3- Surgical removal of the tumor

4- Radiotherapy of the tumor

**Thyroid-stimulating Hormone (TSH)**

Also called thyrotrophin. Stimulates secretion of thyroid hormone & growth of thyroid gland.

**Diagnostic Uses of TSH**

In patients who have been treated surgically for thyroid carcinoma, to test for recurrence.

**Adrenocorticotropin (ACTH)**

Stimulates cortisol secretion by the adrenal cortex & promotes growth of adrenal cortex.

**Diagnostic use**

As a test of the capacity of the adrenal cortex to produce cortisol

**Follicle –stimulating hormone (FSH)**

* Females: stimulates growth of ovarian follicles, promotes secretion of estrogen by ovaries.
* Males: required for sperm production

**Leutinizing hormone (LH)**

* Females: responsible for ovulation, formation of corpus luteum in the ovary, and regulation of ovarian secretion of female sex hormone.
* Males: stimulates cell in the testes to secrete testosterone.

**Prolactin**

* Females: stimulates breast development and milk production.
* Males: involved in testicular function.

**Posterior pituitary Hormones**

**Oxytocin & Vasopressin**

They are synthesized in the hypothalamus & transported to the posterior Pituitary gland.

**Oxytocin**

* Stimulate uterine contractions & is used IV to induce labor.
* Induces the release of milk
* Suckling sends a message to the hypothalamus via the nervous system to release oxytocin, which further stimulates the milk glands

**Vasopressin (antidiuretic hormone) (ADH)**

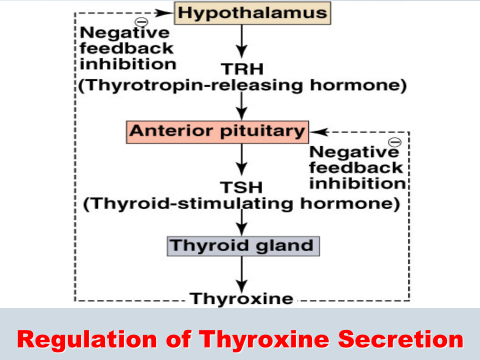
* Increase water reabsorption of kidney.
* If there is a high level of ADH secretion, the kidneys reabsorb water.
* If there is a low level of ADH secretion, the kidneys release water in dilute urine.

**Thyroid and Parathyroid Glands**

**Thyroid gland**

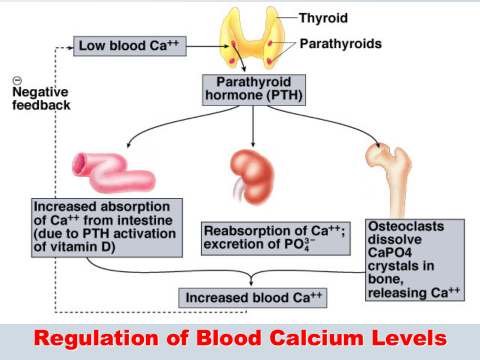
Thyroxine helps set basal metabolic rate by stimulating the rate of cell respiration.

In children, thyroid hormones also promote growth and stimulate maturation of the central nervous system.



**Parathyroid gland**

Produces parathyroid hormone (PTH). Stimulates osteoclasts in bone to dissolve calcium phosphate crystals and release Ca++ into the blood.



**Adrenal Glands**

Each gland composed of inner portion (adrenal medulla) and outer layer (adrenal cortex).

**Adrenal medulla**

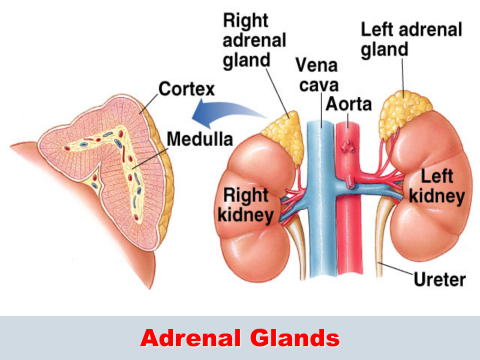
Receives sympathetic stimulation of the autonomic nervous system, and secretes epinephrine and norepinephrine in response.

**Adrenal cortex**

Hormones from adrenal cortex are collectively referred to as corticosteroids.

Cortisol maintains glucose homeostasis, and modulates some aspects of the immune response.

Aldosterone stimulates the kidneys to reabsorb Na+ and secrete K+ into the urine.



Other Endocrine Glands

* + - **Ovaries and testes** produce androgen, and are responsible for secondary sexual characteristics
    - **Pineal gland** secretes melatonin & regulates biological clocks

**Diabetes Mellitus**

**Definition, Classification, and Epidemiology**

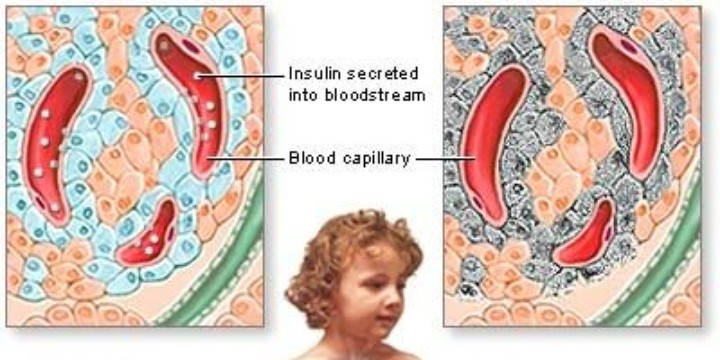
Diabetes is a chronic condition caused by a relative or an absolute lack of insulin. Its hallmark clinical characteristics are symptomatic glucose intolerance resulting in hyperglycemia and alterations in lipid and protein metabolism. Over the long term, these metabolic abnormalities contribute to the development of complications such as retinopathy, nephropathy, and neuropathy.

Genetically, etiologically, and clinically, diabetes is a heterogeneous group of disorders. Nevertheless, most cases of diabetes mellitus can be assigned to type 1 or type 2 diabetes. The term gestational diabetes mellitus (GDM) is used to describe glucose intolerance that has its onset during pregnancy. Subclinical glucose intolerance or “prediabetes” is identified as impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT).

**Type 1 Diabetes Mellitus or Insulin Dependent DM (IDDM)**

**Pathogenesis**

The loss of insulin secretion in type 1 diabetes mellitus results from autoimmune destruction of the insulin-producing β-cells in the pancreas, which is thought to be triggered by environmental factors, such as viruses or toxins, in genetically susceptible individuals.



Type 1 diabetes is responsible for most cases of diabetes in children up to the age of 12 years.

**Clinical Presentation**

When plasma glucose concentrations exceed the normal renal threshold of approximately 180 mg/dL (10 mmol/L), **glucosuria** results in an osmotic diuresis, producing the classic symptoms of **polyuria** with compensatory **polydipsia.**

If symptoms are untreated, **weight loss** occurs as glucose calories are lost in the urine and body fat and protein stores are broken down owing to increased rates of **lipolysis and proteolysis.** Muscle begins to metabolize its own glycogen stores and fatty acids for fuel, and the liver begins to metabolize free fatty acids that are released in response to epinephrine and low insulin concentrations.

An absolute lack of insulin may cause excessive mobilization of free fatty acids to the liver, where they are metabolized to ketones. This can result in **ketoacidosis.**

**Honeymoon Period**

Within days or weeks after the initial diagnosis, many patients with type 1 diabetes experience an apparent remission, which is reflected by decreased blood glucose concentrations and markedly decreased insulin requirements. This is called the honeymoon period because it may last for only a few weeks to months.

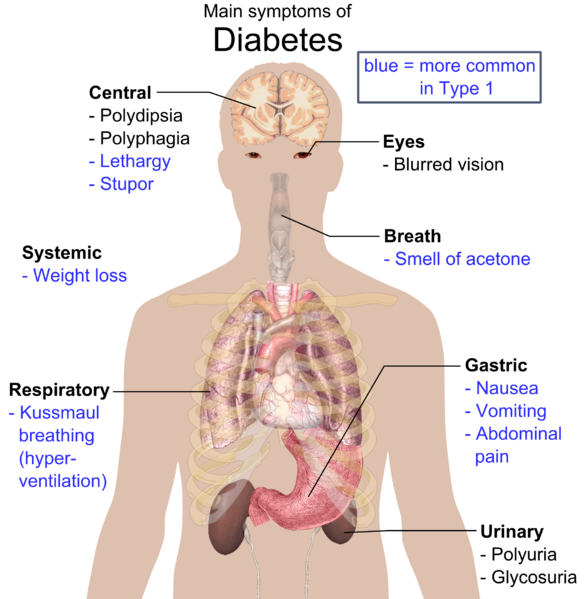
**Type 2 Diabetes Mellitus or non-insulin dependent DM (NIDDM)**

**Pathogenesis**

Type 2 diabetes is characterized by impaired insulin secretion and resistance to insulin action. In the presence of insulin resistance, glucose utilization by tissues is impaired, hepatic glucose production is increased, and excess glucose accumulates in the circulation. This hyperglycemia stimulates the pancreas to produce more insulin in an attempt to overcome insulin resistance. Genetic predisposition may play a role in the development of type 2 diabetes. Environmental factors such as obesity and a sedentary lifestyle also contribute.

**Clinical Presentation**

Type 2 diabetes is typically diagnosed incidentally during a routine physical examination or when the patient seeks attention for another complaint. This is because symptoms are so mild and their onset so gradual that they can easily be “explained away.” When giving a history of their illness, people with type 2 diabetes acknowledge **fatigue, polyuria, and polydipsia.**

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**Main symptoms of DM**

**Gestational Diabetes Mellitus**

GDM affects about 7% of all pregnancies and is defined as any carbohydrate intolerance with onset or first recognition during pregnancy. The onset of diabetes during pregnancy and its duration affect the prognosis for a good obstetric and perinatal outcome.

**Treatment of diabetes**

There are three major components to the treatment of diabetes: diet, drugs (insulin and oral hypoglycemic agents, and other antihyperglycemic agents), and exercise. Each of these components interacts with the others to the extent that no assessment and modification of one can be made without knowledge of the other two.

**Medical Nutrition Therapy**

**Principles**

Medical Nutrition Therapyplays a crucial role in the therapy of all individuals with diabetes. Unfortunately, patient acceptance and adherence to diet and meal planning is often poor, but revised evidence-based recommendations that are more flexible than previous approaches offer new opportunities to increase the effectiveness of nutrition therapy.

**Nutrition Therapy and Type 1 DM**

For patients with type 1 diabetes taking fixed doses of insulin, a meal plan is designed to provide adequate carbohydrates timed to match the peak action of exogenously administered mealtime insulin. Regularly scheduled meals and snacks should contain consistent carbohydrate amounts, which are required to prevent hypoglycemic reactions.

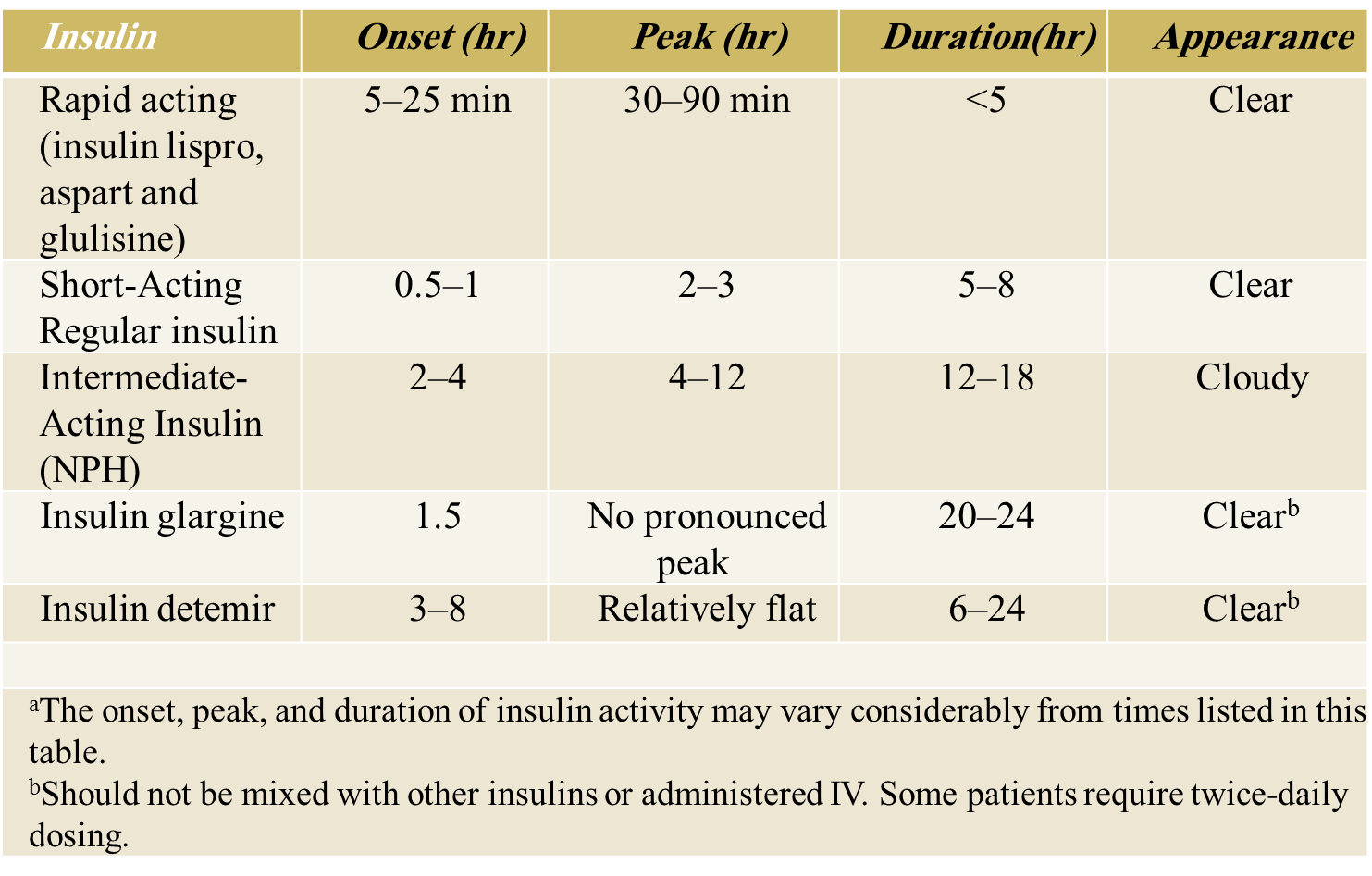
**Nutrition Therapy and Type 2 DM**

For patients with type 2 diabetes, meal plans emphasize normalizing plasma glucose and lipid levels as well as maintaining a normal BP to prevent or mitigate cardiovascular morbidity. Although weight loss reduces insulin resistance and improves glycemic control, traditional dietary strategies incorporating hypocaloric diets have not been effective in achieving long-term weight loss. A sustainable weight loss of 5% to 7% can be achieved within structured programs that emphasize lifestyle changes, physical activity, and food intake that modestly reduces caloric and fat intake.

**Insulin**

Insulin is a hormone secreted from the pancreatic β-cell in response to glucose and other stimulants (e.g., amino acids, free fatty acids, gastric hormones, parasympathetic stimulation, β-adrenergic stimulation). In the storage granule of the β-cell, the connecting or C-peptide is cleaved from proinsulin to produce equimolar amounts of insulin and C-peptide. Thus, measurable C-peptide levels indicate the presence of endogenously produced insulin and functioning β-cells.

**Insulin Pharmacodynamics**



**Adverse Effects of Insulin**

Hypoglycemia is a blood glucose concentration below 60 mg/dL (<2.7 mmol/L), and its occurrence is potentially fatal if not promptly recognized and treated. Symptoms are conventionally divided into two categories: neurogenic (or autonomic) and neuroglycopenic.

Autonomic symptoms include **sweating, intense hunger, palpitations, tremor, tingling, and anxiety.** Epinephrine is thought to mediate many of the neurogenic responses to hypoglycemia.

Neuroglycopenic symptoms resulting from neuronal fuel deprivation (glucose) include **difficulty concentrating; lethargy; confusion; agitation; weakness; and possibly, slurred speech, dizziness, and fainting. Profound behavioral changes, seizures, and coma** are more severe manifestations of neuroglycopenia.

**Treatment of Hypoglycemia**

Mild Hypoglycemia:

Most hypoglycemic reactions are managed readily with the equivalent of 10 to 20 g of glucose.

Moderate to Severe Hypoglycemia:

1. Glucagon can be injected by the SC or IM route.
2. Intravenous Glucose: If glucagon is unavailable, the patient should be taken to the hospital's emergency department, and treated with IV glucose (~10–25 g administered as 20–50 mL of 50% dextrose over 1–3 minutes) in preference to glucagon. Following the bolus injection of glucose, IV glucose (5–10 g/hour) should be continued until the patient has gained consciousness and is able to eat.

**Treatment of Type 2 Diabetes: Antidiabetic Agents**

1. Biguanides
2. Sulfonylureas
3. Nonsulfonylurea Insulin Secretagogues (Glinides)
4. Thiazolidinediones
5. Glucosidase Inhibitors

**Biguanides**

Metformin (Glucophage)

**Adverse Effects**

1. Gastrointestinal Effects
2. Lactic Acidosis

**Contraindications and Precautions**

1. Patients with renal impairment
2. hepatic disease
3. congestive heart failure

**Sulfonylureas**

* The three first-generation sulfonylureas (chlorpropamide, tolazamide, and tolbutamide).
* Second-generation sulfonylureas; Glipizide, Glyburide, Glynase, and Glimepiride.

**Adverse Effects**

1. Hypoglycemia(particularly for those that are long acting)
2. Weight gain.

**Contraindications and Precautions**

* 1. Type 1 diabetes
  2. Pregnancy or breast-feeding, because these agents (except glyburide) can cross the placental barrier and can be excreted into breast milk
  3. Documented hypersensitivity to sulfonylureas
  4. Severe hepatic or renal dysfunction
  5. Severe, acute intercurrent illness (e.g., infection, MI), surgery, or other stress that can unduly affect blood glucose control

**Nonsulfonylurea Insulin Secretagogues (Glinides)**

Repaglinide and nateglinide are nonsulfonylurea insulin secretagogues (i.e., they stimulate insulin secretion). They belong to a class of agents referred to as meglitinides and amino acid derivatives, respectively.

**Thiazolidinediones (TZD)**

Rosiglitazone and pioglitazone were approved in 1999. The TZDs are often referred to as **insulin sensitizers.**

**Adverse Effects**

1. Hepatotoxicity
2. Hematologic Effects
3. Weight Gain
4. Vascular and Cardiovascular Effects

**Contraindications and Precautions**

1. Type 1 diabetes
2. Patients with type 2 diabetes using insulin: due to the increased risk of developing edema.
3. Preexisting hepatic disease
4. Symptomatic or severe CHF
5. Premenopausal anovulatory women
6. History of hypersensitivity to TZDs.

**Glucosidase Inhibitors**

Acarbose (Precose) and miglitol (Glyset) are the two available oral agents in the α-glucosidase inhibitor class of antidiabetic agents.