DISORDERS OF LIPOPROTEIN METABOLISM

- Overview of Cholesterol and Lipid Disorders
- Complications of abnormal lipid levels
- Diagnosing Cholesterol Disorders
- Treatment Options

1. EATING DISORDER

- What is an Eating Disorder (ED)?
- Types of Disordered Eating
- Causes of Disordered Eating
- Treatment for Disordered Eating
- Signs & Symptoms of an Eating Disorder

2. OBESITY

- Definition
- Etiology of obesity
- Symptoms
- Causes
- Risk factors
- Complications/ Disorders of Obesity

3. DISORDERS OF GROWTH

- Length

- Short Stature Due To Endocrine Causes
- Tall Stature Due To Endocrine Disorders

- Weight
- Body Composition
- Tooth Eruption
- Head Circumference

4. DISORDER OF PUBERTY

- EARLY PUBERTY (PRECOCIOUS PUBERTY)

- Types of Precocious Puberty
- Diagnosis
- Treatment

- **DELAYED PUBERTY OR ABSENT PUBERTY (SEXUAL INFANTILISM)**

- Causes
- Symptoms
- Diagnosis
- Treatment

5. ENDOCRINE HYPERTENSION

- Endocrine Hypertension Disorders

DISORDERS OF LIPOPROTEIN METABOLISM

Lipids—fats made up of cholesterol, triglycerides and other fats—travel in the bloodstream as part of particles that contain specialized proteins. High lipid levels in the blood increase a person's risk for heart attack, stroke, peripheral vascular disease and other cardiovascular diseases. Lowering cholesterol levels lowers one's risk of these diseases. In some cases, rare genetic disorders affecting lipids may also lead to harm and require specialist attention.

Overview of Cholesterol and Lipid Disorders

Important fats (lipids) found in the blood are

- Cholesterol
- Triglycerides

Cholesterol is an essential component of cell membranes, of brain and nerve cells, and of bile, which helps the body absorb fats and fat-soluble vitamins. The body uses cholesterol to make vitamin D and various hormones, such as estrogen, testosterone, and cortisol. The body can produce all the cholesterol that it needs, but it also obtains cholesterol from food.

Triglycerides, which are contained in fat cells, can be broken down, and then used to provide energy for the body's metabolic processes, including growth. Triglycerides are produced in the intestine and liver from smaller fats called fatty acids. Some types of fatty acids are made by the body, but others must be obtained from food.

Fats, such as cholesterol and triglycerides, cannot circulate freely in the blood, because blood is mostly water. To be able to circulate in blood, cholesterol and triglycerides are packaged with proteins and other substances to form particles called lipoproteins.

There are different types of lipoproteins. Each type has a different purpose and is broken down and excreted in a slightly different way. Lipoproteins include

- Chylomicrons
- Very low density lipoproteins (VLDL)
- Low-density lipoproteins (LDL)
- High-density lipoproteins (HDL)

Cholesterol transported by LDL is called LDL cholesterol, and cholesterol transported by HDL is called HDL cholesterol.

The body can regulate lipoprotein levels (and therefore lipid levels) by increasing or decreasing the production rate of lipoproteins. The body can also regulate how quickly lipoproteins enter and are removed from the bloodstream.

Levels of cholesterol and triglycerides vary considerably from day to day. From one measurement to the next, cholesterol levels can vary by about 10%, and triglyceride levels can vary by up to 25%.

Lipid levels may be

- Too high (dyslipidemia)
- Too low (hypolipidemia)

Lipid levels may become abnormal because of changes that occur with aging, various disorders (including inherited ones), use of certain drugs, or lifestyle (such as consuming a diet high in saturated fat, being physically inactive, or being overweight).

Complications of abnormal lipid levels

Abnormal levels of lipids (especially cholesterol) can lead to long-term problems, such as atherosclerosis. Generally, a high total cholesterol level (which includes LDL, HDL, and VLDL cholesterol), particularly a high level of LDL (the "bad") cholesterol, increases the risk of atherosclerosis and thus the risk of heart attack or stroke. However, not all types of cholesterol increase this risk. A high level of HDL (the "good") cholesterol may decrease risk, and conversely, a low level of HDL cholesterol may increase risk.

The effect of triglyceride levels on the risk of heart attack is less clear-cut. But very high levels of triglycerides (higher than 500 milligrams per deciliter of blood, or mg/dL) can increase the risk of pancreatitis.

Diagnosing Cholesterol Disorders

Lipid disorders are diagnosed through a blood test called a lipid profile. A lipid profile measures total cholesterol, HDL (“good”) cholesterol, LDL (“bad”) cholesterol, triglycerides and certain proteins.

An evaluation to assess a patient’s risk for cardiovascular disease and atherosclerosis is also important. Evaluations may be needed when a patient:

- Has trouble lowering his or her cholesterol level with medication
- Is unable to tolerate statins, a type of medication used to lower cholesterol
- Has a genetic disorder that affects lipid levels, such as one that causes high cholesterol or high triglyceride levels from birth, or other lipid abnormalities, such as sitosterolemia

- Has severe hypertriglyceridemia and is at risk for pancreatitis, which carries a high risk of complications and death

Patients may also be screened for secondary disorders, such as hypothyroidism, uncontrolled diabetes, obesity, kidney disease and other conditions that can worsen lipid disorders. Identifying and controlling these disorders can help in overall cholesterol control.

Treatment Options

Treatment for lipid disorders is aimed at intense management of cardiovascular risks to prevent heart attacks, stroke and peripheral vascular disease. Endocrinologists treat most patients using a combination of diet, exercise and medication.

1. **Medical Nutrition Therapy**

All patients require nutrition therapy as part of their treatment. Medical nutrition therapy is used to improve diet and dietary habits, as these can have a significant impact on the blood lipid levels. A dietitian assesses the patient's diet, nutrition and lifestyle, provides nutrition counseling, and discusses how to manage lifestyle factors that affect diet.

2. **Medication**

Medicines that manage blood cholesterol levels may be prescribed. Many of these have been proven to be effective in large scientific studies.

3. **Exercise Plan**

Exercise is part of an overall plan to improve cardiovascular fitness, improve symptom control in people with peripheral vascular disease and improve overall health.

4. **Follow-up Visits**

Follow-up visits after treatment begins are important to assess lipid levels, to determine if patients are tolerating medication and meeting their goals to lower lipid levels, and to assess development of cardiovascular disease.

EATING DISORDER AND OBESITY

What is an Eating Disorder (ED)?

Eating Disorders describe illnesses that are characterized by irregular eating habits and severe distress or concern about body weight or shape.

Eating disturbances may include inadequate or excessive food intake which can ultimately damage an individual's well-being. The most common forms of eating disorders include Anorexia Nervosa, Bulimia Nervosa, and Binge Eating Disorder and affect both females and males.

Disordered eating issues can develop during any stage in life but typically appear during the teen years or young adulthood. Classified as a medical illness, appropriate treatment can be highly effectual for many of the specific types of eating disorders.

Although these conditions are treatable, the symptoms and consequences can be detrimental and deadly if not addressed. Eating disorders commonly coexist with other conditions, such as anxiety disorders, substance abuse, or depression.

Types of Disordered Eating

The three most common types of Eating Disorders are as follows:

1. **Anorexia Nervosa**-The male or female suffering from anorexia nervosa will typically have an obsessive fear of gaining weight, refusal to maintain a healthy body weight and an unrealistic perception of body image. Many people with anorexia nervosa will fiercely limit the quantity of food they consume and view themselves as overweight, even when they are clearly underweight. Anorexia can have damaging health effects, such as brain damage, multi-organ failure, bone loss, heart difficulties, and infertility. The risk of death is highest in individuals with this disease.
2. **Bulimia Nervosa**-This eating disorder is characterized by repeated binge eating followed by behaviors that compensate for the overeating, such as forced vomiting, excessive exercise, or extreme use of laxatives or diuretics. Men and women who suffer from Bulimia may fear weight gain and feel severely unhappy with their body size and shape. The binge-eating and purging cycle is typically done in secret, creating feelings of shame, guilt, and lack of control. Bulimia can have injuring effects, such as gastrointestinal problems, severe dehydration, and heart difficulties resulting from an electrolyte imbalance.
3. **Binge Eating Disorder-** Individuals who suffer from Binge Eating Disorder will frequently lose control over his or her eating. Different from bulimia nervosa however, episodes of binge-eating are not followed by compensatory behaviors, such as purging, fasting, or excessive exercise. Because of this, many people suffering from BED may be

obese and at an increased risk of developing other conditions, such as cardiovascular disease. Men and women who struggle with this disorder may also experience intense feelings of guilt, distress, and embarrassment related to their binge-eating, which could influence the further progression of the eating disorder.

Causes of Disordered Eating

EDs are complex disorders, influenced by a facet of factors. Though the exact cause of eating disorders is unknown, it is generally believed that a combination of biological, psychological, and/or environmental abnormalities contribute to the development of these illnesses.

Examples of biological factors include:

- Irregular hormone functions
- Genetics (the tie between eating disorders and one's genes is still being heavily researched, but we know that genetics is a part of the story).
- Nutritional deficiencies

Examples of psychological factors include:

- Negative body image
- Poor self-esteem

Examples of environmental factors that would contribute to the occurrence of eating disorders are:

- Dysfunctional family dynamic
- Professions and careers that promote being thin and weight loss, such as ballet and modeling
- Aesthetically oriented sports, where an emphasis is placed on maintaining a lean body for enhanced performance.
    - Examples include:
        - Rowing
        - Diving
        - Ballet
        - Gymnastics
        - Wrestling
        - Long distance running
- Family and childhood traumas: childhood sexual abuse, severe trauma
- Cultural and/or peer pressure among friends and co-workers
- Stressful transitions or life changes

Signs & Symptoms of an Eating Disorder

A man or woman suffering from an eating disorder may reveal several signs and symptoms, some which are:

- Chronic dieting despite being hazardously underweight
- Constant weight fluctuations
- Obsession with calories and fat contents of food

- Engaging in ritualistic eating patterns, such as cutting food into tiny pieces, eating alone, and/or hiding food
- Continued fixation with food, recipes, or cooking; the individual may cook intricate meals for others but refrain from partaking
- Depression or lethargic stage
- Avoidance of social functions, family, and friends. May become isolated and withdrawn
- Switching between periods of overeating and fasting

Treatment for Disordered Eating

Treatment for an ED is usually comprised of one or more of the following and addressed with medical doctors, nutritionists, and therapists for complete care:

- Medical Care and Monitoring-The highest concern in the treatment of eating disorders is addressing any health issues that may have been a consequence of eating disordered behaviors.
- Nutrition: This would involve weight restoration and stabilization, guidance for normal eating, and the integration of an individualized meal plan.
- Therapy: Different forms of psychotherapy, such as individual, family, or group, can be helpful in addressing the underlying causes of eating disorders. Therapy is a fundamental piece of treatment because it affords an individual in recovery the opportunity to address and heal from traumatic life events and learn healthier coping skills and methods for expressing emotions, communicating and maintaining healthy relationships.
- Medications: Some medications may be effective in helping resolve mood or anxiety symptoms that can occur with an eating disorder or in reducing binge-eating and purging behaviors.

OBESITY

Definition

Obesity is a complex disease involving an excessive amount of body fat (adipose tissue mass). Obesity isn't just a cosmetic concern. It is a medical problem that increases your risk of other diseases and health problems, such as heart disease, diabetes, high blood pressure and certain cancers.

There are many reasons why some people have difficulty avoiding obesity. Usually, obesity results from a combination of inherited factors, combined with the environment and personal diet and exercise choices.

Etiology of obesity

Although the molecular pathways regulating energy balance are beginning to be illuminated, the causes of obesity remain elusive. In part, this reflects the fact that obesity is a heterogeneous group of disorders. At one level, the pathophysiology of obesity seems simple: a chronic excess of nutrient intake relative to the level of energy expenditure. However, due to the complexity of the neuroendocrine and metabolic systems that regulate energy intake, storage, and expenditure, it has been difficult to quantitate all the relevant parameters (e.g., food intake and energy expenditure) over time in human subjects.

Symptoms

Obesity is diagnosed when your body mass index (BMI) is 30 or higher. To determine your body mass index, divide your weight in pounds by your height in inches squared and multiply by 703. Or divide your weight in kilograms by your height in meters squared.

BMI	**Weight status**
Below 18.5	Underweight
18.5-24.9	Normal
25.0-29.9	Overweight
30.0 and higher	Obesity

Causes

Although there are genetic, behavioral, metabolic and hormonal influences on body weight, obesity occurs when you take in more calories than you burn through exercise and normal daily activities. Your body stores these excess calories as fat.

Most Americans' diets are too high in calories — often from fast food and high-calorie beverages. People with obesity might eat more calories before feeling full, feel hungry sooner, or eat more due to stress or anxiety.

Risk factors

Obesity usually results from a combination of causes and contributing factors:

1. Family inheritance and influences

The genes you inherit from your parents may affect the amount of body fat you store, and where that fat is distributed. Genetics may also play a role in how efficiently your body converts food into energy, how your body regulates your appetite and how your body burns calories during exercise.

Obesity tends to run in families. That's not just because of the genes they share. Family members also tend to share similar eating and activity habits.

2. Lifestyle choices

- **Unhealthy diet.** A diet that's high in calories, lacking in fruits and vegetables, full of fast food, and laden with high-calorie beverages and oversized portions contributes to weight gain.
- **Liquid calories.** People can drink many calories without feeling full, especially calories from alcohol. Other high-calorie beverages, such as sugared soft drinks, can contribute to significant weight gain.
- **Inactivity.** If you have a sedentary lifestyle, you can easily take in more calories every day than you burn through exercise and routine daily activities. Looking at computer, tablet and phone screens is a sedentary activity. The number of hours you spend in front of a screen is highly associated with weight gain.

3. Certain diseases and medications

In some people, obesity can be traced to a medical cause, such as Prader-Willi syndrome, Cushing syndrome and other conditions. Medical problems, such as arthritis, also can lead to decreased activity, which may result in weight gain.

Some medications can lead to weight gain if you don't compensate through diet or activity. These medications include some antidepressants, anti-seizure medications, diabetes medications, antipsychotic medications, steroids and beta blockers.

4. Social and economic issues

Social and economic factors are linked to obesity. Avoiding obesity is difficult if you don't have safe areas to walk or exercise. Similarly, you may not have been taught healthy ways of cooking,

or you may not have access to healthier foods. In addition, the people you spend time with may influence your weight — you're more likely to develop obesity if you have friends or relatives with obesity.

5. Age

Obesity can occur at any age, even in young children. But as you age, hormonal changes and a less active lifestyle increase your risk of obesity. In addition, the amount of muscle in your body tends to decrease with age. Generally, lower muscle mass leads to a decrease in metabolism. These changes also reduce calorie needs, and can make it harder to keep off excess weight. If you don't consciously control what you eat and become more physically active as you age, you'll likely gain weight.

6. Other factors

- **Pregnancy.** Weight gain is common during pregnancy. Some women find this weight difficult to lose after the baby is born. This weight gain may contribute to the development of obesity in women. Breast-feeding may be the best option to lose the weight gained during pregnancy.
- **Quitting smoking.** Quitting smoking is often associated with weight gain. And for some, it can lead to enough weight gain to qualify as obesity. Often, this happens as people use food to cope with smoking withdrawal. In the long run, however, quitting smoking is still a greater benefit to your health than is continuing to smoke. Your doctor can help you prevent weight gain after quitting smoking.
- **Lack of sleep.** Not getting enough sleep or getting too much sleep can cause changes in hormones that increase your appetite. You may also crave foods high in calories and carbohydrates, which can contribute to weight gain.
- **Stress.** Many external factors that affect your mood and well-being may contribute to obesity. People often seek more high-calorie food when experiencing stressful situations.
- **Microbiome.** Your gut bacteria are affected by what you eat and may contribute to weight gain or difficulty losing weight.
- **Previous attempts to lose weight.** Previous attempts of weight loss followed by rapid weight regain may contribute to further weight gain. This phenomenon, sometimes called yo-yo dieting, can slow your metabolism.

Even if you have one or more of these risk factors, it doesn't mean that you're destined to develop obesity. You can counteract most risk factors through diet, physical activity and exercise, and behavior changes.

Complications/ Disorders of Obesity

People with obesity are more likely to develop a number of potentially serious health problems, including:

1. **Heart disease and strokes.** Obesity makes you more likely to have high blood pressure and abnormal cholesterol levels, which are risk factors for heart disease and strokes.
2. **Type 2 diabetes.** Obesity can affect the way your body uses insulin to control blood sugar levels. This raises your risk of insulin resistance and diabetes.
3. **Certain cancers.** Obesity may increase your risk of cancer of the uterus, cervix, endometrium, ovary, breast, colon, rectum, esophagus, liver, gallbladder, pancreas, kidney and prostate.
4. **Digestive problems.** Obesity increases the likelihood that you'll develop heartburn, gallbladder disease and liver problems.
5. **Gynecological and sexual problems.** Obesity may cause infertility and irregular periods in women. Obesity also can cause erectile dysfunction in men.
6. **Sleep apnea.** People with obesity are more likely to have sleep apnea, a potentially serious disorder in which breathing repeatedly stops and starts during sleep.
7. **Osteoarthritis.** Obesity increases the stress placed on weight-bearing joints, in addition to promoting inflammation within the body. These factors may lead to complications such as osteoarthritis.

DISORDERS OF GROWTH

GROWTH

Physical growth includes attainment of full height and appropriate weight and an increase in size of all organs (except lymphatic tissue, which decreases in size). Growth from birth to adolescence occurs in 2 distinct phases:

- Phase 1 (from birth to about age 1 to 2 years): This phase is one of rapid growth, although the rate of growth decreases over that period.
- Phase 2 (from about 2 years to the onset of puberty): In this phase, growth occurs in relatively constant annual increments.

Puberty is the process of physical maturation from child to adult. Adolescence defines an age group; puberty occurs during adolescence. At puberty, a 2nd growth spurt occurs, affecting boys and girls slightly differently.

From birth until age 2 years, it is recommended that all growth parameters be charted using standard growth charts from the WHO. After age 2, growth parameters are charted using growth charts from the CDC (Centers for Disease Control and Prevention).

Length

Length is measured in children too young to stand; height is measured once the child can stand. In general, length in normal-term infants increases about 30% by 5 months and > 50% by 12 months; infants grow about 25 cm during the first year, and height at 5 years is about double the birth length. In most boys, half the adult height is attained by about age 2; in most girls, height at 19 months is about half the adult height.

Rate of change in height (height velocity) is a more sensitive measure of growth than time-specific height measures. In general, healthy term infants and children grow about 2.5 cm/month between birth and 6 months, 1.3 cm/month from 7 to 12 months, and about 7.6 cm/year between 12 months and 10 years.

Before 12 months, height velocity varies and is due in part to prenatal factors (eg, prematurity). After 12 months, height is mostly genetically determined, and height velocity stays nearly constant until puberty; a child’s height relative to peers tends to remain the same.

Some small-for-gestational-age infants tend to be shorter throughout life than infants whose size is appropriate for their gestational age. Boys and girls show little difference in height and growth rate during infancy and childhood.

Extremities grow faster than the trunk, leading to a gradual change in relative proportions; the crown-to-pubis/pubis-to-heel ratio is 1.7 at birth, 1.5 at 12 months, 1.2 at 5 years, and 1.0 after 7 years.

Short Stature Due To Endocrine Causes

There are many causes of decreased childhood growth and short adult height.

- **Growth hormone deficiency and its variants**

The incidence of GH deficiency is estimated to be between 1:4000 and 1:3500, so the disorder should not be considered rare. Most patients with idiopathic GH deficiency lack GHRH(Growth hormone–releasing hormone). One autopsied GH-deficient patient had an adequate number of pituitary somatotrophs that contained considerable GH stores. Thus, the pituitary gland produced GH, but it could not be released. Long-term treatment of such patients with GHRH can cause GH release and increase growth, but this therapy is not presently in use. Patients with pituitary tumors or those rare patients with congenital absence of the pituitary gland lack somatotrophs. Several kindreds have been described that lack various regions of the GH gene (responsible for producing GH). Patients with classic GH deficiency have short stature, increased fat mass leading to a chubby or cherubic appearance with immature facial appearance, immature high-pitched voice, and delay in skeletal maturation.

- **Acquired Growth Hormone Deficiency**

Onset of GH deficiency in late childhood or adolescence, particularly if accompanied by other pituitary hormone deficiencies, is ominous and may be due to a hypothalamic-pituitary tumor. The development of posterior pituitary deficiency, in addition to anterior pituitary deficiency, makes a tumor even more likely. The empty sella syndrome is more frequently associated with hypothalamic-pituitary abnormalities in childhood than in adulthood; thus, GH deficiency may be found in affected patients. Some patients, chiefly boys with constitutional delay in growth and adolescence, may have transient GH deficiency on testing before the onset of puberty. When serum testosterone concentrations begin to increase in these patients, GH secretion and growth rate also increase. This transient state may incorrectly suggest bona fide GH deficiency but does not require therapy.

Tall Stature Due To Endocrine Disorders

1. **Pituitary gigantism**

Pituitary gigantism is caused by excess GH secretion before the age of epiphyseal fusion. The increased GH secretion may be due to somatotroph-secreting tumors or constitutive activation of GH secretion as is sometimes found in the McCune-Albright syndrome. Alternatively, it may result from excess secretion of GHRH (Growth hormone–releasing hormone). Patients besides growing excessively rapidly have coarse features, large hands and feet with thick fingers and toes, and often frontal bossing and large jaws. Although this condition is quite rare, the findings appear similar to those observed in the more frequently diagnosed acromegaly (which occurs with GH excess after epiphyseal fusion).

2. **Sexual precocity**

Early onset of estrogen or androgen secretion leads to abnormally increased height velocity. Because bone age is advanced, there is the paradox of the tall child who, because of early epiphyseal closure, is short as an adult. The conditions include complete and incomplete sexual precocity (including virilizing congenital adrenal hyperplasia).

3. **Thyrotoxicosis**

Excessive thyroid hormone, due to endogenous overproduction or overtreatment with exogenous thyroxine, leads to increased growth, advanced bone age, and, if occurring in early life, craniosynostosis. If the condition remains untreated, adult height will be reduced due to early epiphyseal closure.

4. **Infants of diabetic mothers**

Birth weight and size in infants of diabetic mothers are quite usually high, although severely affected, poorly controlled mothers with type 1 diabetes may have infants with IUGR (Intrauterine growth retardation or restriction) due to placental vascular insufficiency. Severe hypoglycemia and hypocalcemia are evident in the affected infants soon after birth. The appearance and size of such infants is so striking that women have been diagnosed with gestational diabetes as a result of giving birth to large affected infants. By 10 years of age, infants of diabetic mothers have an increased prevalence of obesity as well as insulin resistance and all of the comorbidities of the condition.

Weight

Weight follows a similar pattern. Normal-term neonates generally lose 5 to 8% of birth weight in the days after delivery but regain their birth weight within 2 weeks. They then gain 14 to 28 g/day until 3 months, then 4000 g between 3 and 12 months, doubling their birth weight by 5 months, tripling it by 12 months, and almost quadrupling it by 2 years. Between age 2 years and puberty, weight increases 2 kg/year. The recent epidemic of childhood obesity has involved markedly greater weight gain, even among very young children. In general, boys are heavier and taller than girls when growth is complete because boys have a longer prepubertal growth period, increased peak velocity during the pubertal growth spurt, and a longer adolescent growth spurt.

Head Circumference

Head circumference reflects brain size and is routinely measured up to 36 months. At birth, the brain is 25% of adult size, and head circumference averages 35 cm. Head circumference increases an average 1 cm/month during the first year; growth is more rapid in the first 8 months, and by 12 months, the brain has completed half its postnatal growth and is 75% of adult size. Head circumference increases 3.5 cm over the next 2 years; the brain is 80% of adult size by age 3 years and 90% by age 7 years.

Body Composition

Body composition (proportions of body fat and water) changes and affects drug volume of distribution. Proportion of fat increases rapidly from 13% at birth to 20 to 25% by 12 months, accounting for the chubby appearance of most infants. Subsequently, a slow fall occurs until preadolescence, when body fat returns to about 13%. There is a slow rise again until the onset of puberty, when body fat may again fall, especially in boys. After puberty, the percentage generally stays stable in girls, whereas in boys there tends to be a slight decline.

Body water measured as a percentage of body weight is 70% at birth, dropping to 61% at 12 months (about equal to the adult percentage). This change is fundamentally due to a decrease in extracellular fluid from 45% to 28% of body weight. Intracellular fluid stays relatively constant. After age 12 months, there is a slow and variable fall in extracellular fluid to adult levels of about 20% and a rise in intracellular fluid to adult levels of about 40%. The relatively larger amount of body water, its high turnover rate, and the comparatively high surface losses (due to a proportionately large surface area) make infants more susceptible to fluid deprivation than older children and adults.

Tooth Eruption

Tooth eruption is variable, primarily because of genetic factors. On average, normal infants should have 6 teeth by 12 months, 12 teeth by 18 months, 16 teeth by 2 years, and all teeth (20) by 2½ years; deciduous teeth are replaced by permanent teeth between the ages of 5 years and 13 years. Eruption of deciduous teeth is similar in both sexes; permanent teeth tend to appear earlier in girls. Tooth eruption may be delayed by familial patterns or by conditions such as rickets, hypopituitarism, hypothyroidism, or Down syndrome. Supernumerary teeth and congenital absence of teeth are probably normal variants.

DISORDER OF PUBERTY

PUBERTY

Puberty has to be considered a phase in the continuous evolution of the hypothalamic hypophysis gonadal function, which stares in the intrauterine life, continues during puberty with achievement of the final somatic and reproductive stage, which will be maintained during the adult life.

Staring the postnatal period, the gonadostat, both in males and females is inactivated, due to the oversensitive negative feedback, by which small quantities of sexual steroids will inhibit the pituitary, associated with a supra neural suppression of the GnRH producing neurons.

Puberty means the self-activation on the axis due to the decrease of the sensitivity of the feedback mechanism, and also du the spontaneous activation of the pulsatile GnRh secretion.

The end effect of puberty is represented by adult appearance, sexual maturity and complete fertility.

Puberty is preceded by:

1. Adrenarche – adrenal sexual steroids synthesis activation, around 6 years of age, 2 years before puberty onset
2. Decrease of gonadostat inhibition – 1 year before puberty onset
3. Gradual increase of the interactions between hypothalamus = pituitary = gonads

EARLY PUBERTY (PRECOCIOUS PUBERTY)

Precocious puberty is sexual maturation that begins before age 9 in boys or before age 8 in girls.

- The cause of precocious puberty is often unknown, but it may be caused by structural abnormalities or tumors in the brain.
- Symptoms include an early growth spurt and early development of pubic and underarm hair.
- The diagnosis is based on x-rays, blood tests, and imaging tests.
- Treatment depends on the type of precocious puberty but may include hormone therapy.

Types of Precocious Puberty

In precocious puberty, a child's body begins changing into an adult's body earlier than anticipated.

There are three types of precocious puberty:

1. Central precocious puberty
2. Peripheral precocious puberty
3. Incomplete puberty

The causes and symptoms differ between the three types.

1. **Central precocious puberty**

This type of precocious puberty is more common overall and is 5 to 10 times more frequent in girls.

Puberty in this type is triggered by the early release of certain sex hormones (gonadotropins) from the pituitary gland. These hormones cause the ovaries or testes (the sex glands) to mature and enlarge. Once mature, the sex glands begin secreting other sex hormones, such as estrogen or testosterone, which triggers puberty. Physical changes are typically those of normal puberty for a child of that sex, except they begin at an earlier age.

Boys show enlargement of the testes, lengthening of the penis, and development facial, underarm, and pubic hair and they take on a masculine appearance.

Girls develop breasts and pubic hair and/or underarm hair and may begin to menstruate.

In both sexes, there is a growth spurt that leads to a rapid height increase. However, unlike in normal puberty, the rapid height increase in precocious puberty ends early so children are shorter as adults than would be expected.

Doctors do not usually find a cause for the early hormone release, particularly in girls, but sometimes it is caused by a tumor or other abnormality in the brain, typically in the pituitary gland or the hypothalamus (the region of the brain that controls the pituitary gland). **Neurofibromatosis** (a disorder where many fleshy growths of nerve tissue grow under the skin and in other parts of the body) and a few other rare disorders also have been linked to central precocious puberty. Sometimes central precocious puberty is triggered by the use of treatments for certain disorders (such as surgery, radiation, or chemotherapy to treat cancer).

2. **Peripheral precocious puberty**

This type of precocious puberty is much less common. In peripheral precocious puberty, the release of estrogen or testosterone (and testosterone-like hormones called androgens) is not stimulated by gonadotropins from the pituitary gland. Instead, high levels of androgens or estrogen are produced by a tumor or other abnormality in the adrenal gland or in an immature testis or ovary. These hormones do not cause the testes or ovaries themselves to mature but do trigger the development of secondary sex characteristics. Because boys and girls may each produce estrogen or androgen, the physical changes of puberty depend on the hormone produced rather than the child's sex. Thus, tumors and abnormalities that produce estrogen result in growth of breast tissue in boys and girls, whereas those that produce androgens result in growth of pubic and underarm hair, adult body odor, and acne in boys and girls and, in boys, enlargement of the penis (but not the testes).

3. Incomplete puberty

Some children prematurely develop only a few signs of puberty. Typically they have premature breast development (thelarche) or premature pubic hair development (adrenarche) without any of the other changes of puberty such as growth of the testes or ovaries, menstruation, or a growth spurt. Some girls have breast development during the first 2 years of life, but they do not have elevated hormone levels. Children with early pubic hair development often have adult-like body odor and acne. Changes progress slowly.

These early physical changes are not caused by a disorder and only a few children go on to develop actual precocious puberty. Early pubic hair development occurs because the adrenal gland increases the level of androgens it produces. However, levels of gonadotropins and estrogens are not increased with early pubic hair development.

Diagnosis

- X-rays of the hand and wrist
- Blood tests
- Possibly imaging of certain organs

Whenever a child has signs of premature, rapidly progressing, or disordered puberty, doctors take an x-ray of the hand and wrist to estimate bone maturity (called a bone age x-ray).

If x-rays show that a child's bones have a more mature appearance than they should for a typical child of that age, a more complete evaluation usually is indicated. Blood tests are done to determine hormone levels.

For central precocious puberty, doctors may do magnetic resonance imaging (MRI) of the brain to check for tumors of the hypothalamus or pituitary gland.

For peripheral precocious puberty, doctors may do ultrasonography of the pelvis and adrenal glands to check for ovarian or adrenal tumors.

Treatment

- Treatment of cause
- Synthetic hormone therapy

Treatment of precocious puberty is usually not needed for children who have only premature pubic and underarm hair growth, but regular re-examination is needed to check for later development of precocious puberty. Children whose breast development began before age 2 years are evaluated if breast growth remains past age 2.

Treating an identifiable cause of precocious puberty, such as removing a tumor or cyst, may stop the progression of puberty.

When no treatable cause is identified in central precocious puberty, drugs may slow the progression of puberty. The decision to give drugs depends on many factors, including the child's age, how fast puberty is progressing, how fast the child is growing, and how tall doctors think the child will be. The goals of drug treatment are to allow a child to grow to normal adult height and to relieve any anxiety the child feels due to developing sooner than peers. Treatment options include synthetic hormone injections that stop the production of sex hormones. The injections are given monthly or every three months. The hormones can also be given by an implant that is inserted under the skin every 12 months.

Peripheral precocious puberty can be stopped by drugs that block the action of the sex hormones.

DELAYED PUBERTY OR ABSENT PUBERTY (SEXUAL INFANTILISM)

Delayed puberty is defined as absence of the start of sexual maturation at the expected time.

- Most often, children simply develop later than their peers but ultimately develop normally.
- Sometimes, delayed puberty is caused by chronic medical problems, hormonal disorders, radiation therapy or chemotherapy, disordered eating or excessive exercise, genetic disorders, tumors, and certain infections.
- Typical symptoms include a lack of testicular enlargement in boys and a lack of breasts and menstrual periods in girls.
- The diagnosis is based on the results of a physical examination, various laboratory tests, a bone age x-ray, and, if needed, a chromosomal analysis and magnetic resonance imaging.
- Treatment depends on the cause and may include hormone replacement therapy.

The start of sexual maturation (puberty) takes place when the hypothalamus gland begins to secrete a chemical signal called gonadotropin-releasing hormone. The pituitary gland responds to this signal by releasing hormones called gonadotropins, which stimulate the growth of the sex glands (the testes in boys and the ovaries in girls). The growing sex glands secrete the sex hormones testosterone in boys and estrogen in girls. These hormones cause the development of secondary sex characteristics, including facial hair and muscle mass in boys, breasts in girls, and pubic and underarm hair and sexual desire (libido) in both sexes.

Some adolescents do not start their sexual development at the usual age.

In boys, delayed puberty is more common and is defined as

- No enlargement of the testes (testicles) by age 14
- A time lapse of more than 5 years from the start to the completion of growth of the genitals

In girls, delayed puberty is defined as

- No breast development by age 13
- A time lapse of more than 5 years from the beginning of breast growth to the first menstrual period
- No menstruation (amenorrhea) by age 16

Causes

In the majority of cases, delayed puberty represents a normal variation, which may run in the family (also called constitutional delay of puberty). These adolescents have a normal growth rate and are otherwise healthy. Although the growth spurt and puberty are delayed, they eventually proceed normally.

Various disorders, such as diabetes mellitus, inflammatory bowel disease, kidney disease, cystic fibrosis, and anemia, can delay or prevent sexual development. Development may be delayed or absent in adolescents receiving radiation therapy or cancer chemotherapy. Puberty may also be delayed by autoimmune disorders (such as Hashimoto thyroiditis, Addison disease [primary adrenocortical insufficiency], and some disorders that directly affect the ovaries). A tumor that damages the pituitary gland or the hypothalamus can lower the levels of gonadotropins or stop production of the hormones altogether.

In boys, testicular disorders such as injury, for example, resulting from prior twisting of a testis (testicular torsion), or infection (such as mumps) may delay puberty. Adolescents, particularly girls, who become very thin because of excessive exercise or dieting often have delayed puberty, including an absence of menstruation (amenorrhea).

Chromosomal abnormalities, such as Turner syndrome in girls and Klinefelter syndrome in boys, and other genetic disorders can affect the production of sex hormones. One of these genetic disorders, Kallmann syndrome, affects only gonadotropin production (without affecting production of other hormones).

Symptoms

Adolescents who have delayed puberty may be noticeably shorter than their peers, can be teased or bullied, and often need help coping with and managing social concerns. Although adolescents are typically uncomfortable about being different from their peers, boys in particular are likely to feel psychologic stress and embarrassment resulting from delayed puberty.

Diagnosis

- A physical examination
- Bone age x-ray
- Blood tests
- Sometimes magnetic resonance imaging

The initial evaluation of delayed puberty should consist of a complete history and physical examination to evaluate pubertal development, nutritional status, and growth.

Doctors often take x-rays of one or more bones to see the level of bone maturity (called a bone age x-ray).

Doctors may do basic laboratory tests to look for signs of chronic disease, hormone level tests, and possibly a chromosomal analysis.

Doctors usually evaluate boys who have no signs of puberty by age 14 years and girls who have no signs of puberty by age 13 years or who have not menstruated by age 16 years. If these children otherwise appear healthy, they most likely have constitutional delay. The doctor may decide to re-examine these adolescents at 6-month intervals to ensure that puberty begins and progresses normally.

Girls with severely delayed puberty should be evaluated for primary amenorrhea.

Magnetic resonance imaging (MRI) may be done to ensure that there is no brain tumor or structural abnormality in the pituitary gland.

Treatment

- Treatment of cause
- Hormone therapy

The treatment for delayed puberty depends on its cause. When an underlying disorder is the cause of delayed puberty, puberty usually proceeds once the disorder has been treated.

An adolescent who is naturally late in developing needs no treatment, but if the adolescent is severely stressed by delayed or absent development, some doctors may give supplemental sex hormones to begin the process sooner. Treatment is much more common in boys.

If **boys** show no sign of puberty by age 14, they may be given a 4- to 6-month course of testosterone injections once a month. At low doses, testosterone starts puberty, causes the development of some masculine characteristics (virilization), and does not prevent adolescents from reaching their adult height potential.

In **girls,** low doses of estrogen may be started with pills or skin patches.

Genetic disorders cannot be cured, but hormone therapy may help sex characteristics develop.

Surgery may be needed to remove tumors, and these children are at risk of hypopituitarism.

ENDOCRINE HYPERTENSION

Endocrine hypertension is a subset of hypertension caused by hormone imbalance, most frequently involving the pituitary or adrenal gland. Patients who develop hypertension before the age of 30 who have a strong family history of hypertension, adrenal tumors, or develop a low potassium level (hypokalemia) should be screened for endocrine hypertension.

Endocrine Hypertension Disorders

Endocrine hypertension can be caused when glands produce too much or not enough hormone, or when they are affected by tumors.

1. Primary Aldosteronism

The most common form of endocrine hypertension, primary aldosteronism affects an estimated 5 percent to 10 percent of all patients with hypertension and is often under diagnosed. Excessive aldosterone production by the adrenal glands leads to fluid retention, loss of potassium and hypertension. If untreated, hyperaldosteronism may cause an enlarged heart.

Primary aldosteronism is diagnosed through blood and urine tests, and a CT scan of the adrenal glands. In some cases, adrenal vein sampling may be necessary to help differentiate the cause of the primary aldosteronism.

Forms of the disorder include:

- **Conn's syndrome** — a common subtype caused by a single adrenal tumor. Surgery to remove the tumor is an effective treatment.
- **Bilateral adrenal hyperplasia** — a common subtype caused by enlarged adrenal glands. This disorder is best treated with medications such as spironolactone and eplerenone.
- **Primary adrenal hyperplasia** — a rare subtype in which only one gland is enlarged. Surgery is the preferred treatment.
- **Glucocorticoid remediable aldosteronism (GRA)** — a rare subtype caused by a genetic mutation, often occurring in many family members.
- **Familial hyperaldosteronism** — a rare subtype in which about half of each generation develops hyperaldosteronism.

2. Cushing’s Syndrome

Cushing's syndrome occurs when too much cortisol is produced by the adrenal glands. People with Cushing’s syndrome often have other endocrine-related disorders, including diabetes, obesity, hypertension, kidney stones and osteoporosis. Many patients also suffer from depression.

3. Pheochromocytoma

Phecohromocytoma is a rare syndrome caused by tumors of the adrenal glands. These tumors produce excessive amounts of adrenaline, noradrenaline or other catecholamines. Though rare, patients with adrenal tumors should be tested for pheochromocytoma as about 10 percent of tumors are malignant.

Common symptoms are sweating, palpitations and headache, though patients can also have many other symptoms. Patients with a pheochromocytoma may have episodic or sustained hypertension. Some patients experience very high blood pressure readings known as hypertensive crisis, which is a medical emergency.

One in 10 people with pheochromocytoma has tumors located outside the adrenal glands. These extra-adrenal pheochromocytomas are also known as paragangliomas.

Another 10 percent of pheochromocytomas are part of multiple endocrine neoplasia syndromes (MEN syndrome I or II) which are genetic conditions that run in families. MEN syndromes can involve other endocrine organs such as the parathyroid glands, the pituitary, thyroid as well as other organs such as the kidney, pancreas or stomach.

4. Acromegaly

Acromegaly is a tumor of the pituitary gland that leads to excess growth hormone. Symptoms include joint and muscle problems, headache and vision problems. Affected patients tend to have very large hands, feet and tongue, and a prominent jaw. They can develop hypertension and diabetes.

5. Hyperthyroidism or Hypothyroidism

These disorders, if severe and untreated, can be associated with elevated blood pressure. Treatment of the thyroid disorder usually lowers the blood pressure to normal.

6. Other Causes of Endocrine Hypertension and Related Syndromes:

- **Pseudohypoaldosteronism type 2 (Gordon's syndrome)** — patients develop hypertension and have high potassium levels (hyperkalemia)
- **Liddle's syndrome** — a rare genetic form of hypertension in which patients have very low levels of aldosterone (pseudoaldosteronism)
- **Apparent mineralocorticoid excess** (AME) — a rare genetic form of hypertension
- **Licorice ingestion** — high blood pressure and low potassium triggered by eating licorice (usually black).
- **Bartter's syndrome** — detected in infancy or childhood with symptoms of severe low potassium (hypokalemia) and other birth defects. No associated hypertension.
- **Gitelman's syndrome** — milder form of hypokalemia occurring in young adults, often with low magnesium levels as well. No associated hypertension.