Diabetes and Hypertension

Ross Molina

Luci Aleman

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Table of Contents

Chapter 1

Diabetes Mellitus

Diabetes mellitus

Universal blue circle symbol for diabetes

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Diabetes mellitus, often simply referred to as **diabetes**—is a group of metabolic diseases in which a person has high blood sugar, either because the body does not produce enough insulin, or because cells do not respond to the insulin that is produced. This high blood sugar produces the classical symptoms of polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger).

There are three main types of diabetes:

- Type 1 diabetes: results from the body's failure to produce insulin, and presently requires the person to inject insulin. (Also referred to as *insulin-dependent* diabetes mellitus, *IDDM* for short, and *juvenile* diabetes.)
- Type 2 diabetes: results from insulin resistance, a condition in which cells fail to use insulin properly, sometimes combined with an absolute insulin deficiency. (Formerly referred to as *non-insulin-dependent* diabetes mellitus, *NIDDM* for short, and *adult-onset* diabetes.)
- Gestational diabetes: is when pregnant women, who have never had diabetes before, have a high blood glucose level during pregnancy. It may precede development of type 2 DM.

Other forms of diabetes mellitus include congenital diabetes, which is due to genetic defects of insulin secretion, cystic fibrosis-related diabetes, steroid diabetes induced by high doses of glucocorticoids, and several forms of monogenic diabetes.

All forms of diabetes have been treatable since insulin became available in 1921, and type 2 diabetes may be controlled with medications. Both type 1 and 2 are chronic conditions that usually cannot be cured. Pancreas transplants have been tried with limited success in type 1 DM; gastric bypass surgery has been successful in many with morbid obesity and type 2 DM. Gestational diabetes usually resolves after delivery. Diabetes without proper treatments can cause many complications. Acute complications include hypoglycemia, diabetic ketoacidosis, or nonketotic hyperosmolar coma. Serious long-term complications include cardiovascular disease, chronic renal failure, retinal damage. Adequate treatment of diabetes is thus important, as well as blood pressure control and lifestyle factors such as smoking cessation and maintaining a healthy body weight.

As of 2000 at least 171 million people worldwide suffer from diabetes, or 2.8% of the population. Type 2 diabetes is by far the most common, affecting 90 to 95% of the U.S. diabetes population.

Definition

The word diabetes is from the Greek *diabanein* which means to pass through, in reference to the excessive urine produced as a symptom of these diseases. The term *diabetes*, without qualification, usually refers to diabetes mellitus, which roughly translates to excessive sweet urine (known as "glycosuria"). Several rare conditions are also named diabetes. The most common of these is diabetes insipidus in which large amounts of urine are produced (polyuria), which is not sweet (insipidus meaning "without taste" in Latin).

The term "type 1 diabetes" has replaced several former terms, including childhood-onset diabetes, juvenile diabetes, and insulin-dependent diabetes mellitus (IDDM). Likewise, the term "type 2 diabetes" has replaced several former terms, including adult-onset diabetes, obesity-related diabetes, and non-insulin-dependent diabetes mellitus (NIDDM).

Beyond these two types, there is no agreed-upon standard nomenclature. Various sources have defined "type 3 diabetes" as: gestational diabetes, insulin-resistant type 1 diabetes (or "double diabetes"), type 2 diabetes which has progressed to require injected insulin, and latent autoimmune diabetes of adults (or LADA or "type 1.5" diabetes)

Classification

Most cases of diabetes mellitus fall into three broad categories: type 1, type 2, and gestational diabetes. A few other types are described.

Type 1 diabetes

Type 1 diabetes mellitus is characterized by loss of the insulin-producing beta cells of the islets of Langerhans in the pancreas leading to insulin deficiency. This type of diabetes can be further classified as immune-mediated or idiopathic. The majority of type 1 diabetes is of the immune-mediated nature, where beta cell loss is a T-cell mediated autoimmune attack. There is no known preventive measure against type 1 diabetes, which causes approximately 10% of diabetes mellitus cases in North America and Europe. Most affected people are otherwise healthy and of a healthy weight when onset occurs. Sensitivity and responsiveness to insulin are usually normal, especially in the early stages. Type 1 diabetes can affect children or adults but was traditionally termed "juvenile diabetes" because it represents a majority of the diabetes cases in children.

Type 2 diabetes

Type 2 diabetes mellitus is characterized by insulin resistance which may be combined with relatively reduced insulin secretion. The defective responsiveness of body tissues to insulin is believed to involve the insulin receptor. However, the specific defects are not known. Diabetes mellitus due to a known defect are classified separately. Type 2 diabetes is the most common type.

In the early stage of type 2 diabetes, the predominant abnormality is reduced insulin sensitivity. At this stage hyperglycemia can be reversed by a variety of measures and medications that improve insulin sensitivity or reduce glucose production by the liver.

Gestational diabetes

Gestational diabetes mellitus (GDM) resembles type 2 diabetes in several respects, involving a combination of relatively inadequate insulin secretion and responsiveness. It occurs in about 2%–5% of all pregnancies and may improve or disappear after delivery. Gestational diabetes is fully treatable but requires careful medical supervision throughout the pregnancy. About 20%–50% of affected women develop type 2 diabetes later in life.

Even though it may be transient, untreated gestational diabetes can damage the health of the fetus or mother. Risks to the baby include macrosomia (high birth weight), congenital cardiac and central nervous system anomalies, and skeletal muscle malformations.

Increased fetal insulin may inhibit fetal surfactant production and cause respiratory distress syndrome. Hyperbilirubinemia may result from red blood cell destruction. In severe cases, perinatal death may occur, most commonly as a result of poor placental perfusion due to vascular impairment. Labor induction may be indicated with decreased placental function. A cesarean section may be performed if there is marked fetal distress or an increased risk of injury associated with macrosomia, such as shoulder dystocia.

A 2008 study completed in the U.S. found that the number of American women entering pregnancy with preexisting diabetes is increasing. In fact the rate of diabetes in expectant mothers has more than doubled in the past 6 years. This is particularly problematic as diabetes raises the risk of complications during pregnancy, as well as increasing the potential that the children of diabetic mothers will also become diabetic in the future.

Other types

Pre-diabetes indicates a condition that occurs when a person's blood glucose levels are higher than normal but not high enough for a diagnosis of type 2 diabetes. Many people destined to develop type 2 diabetes spend many years in a state of pre-diabetes which has been termed "America's largest healthcare epidemic."

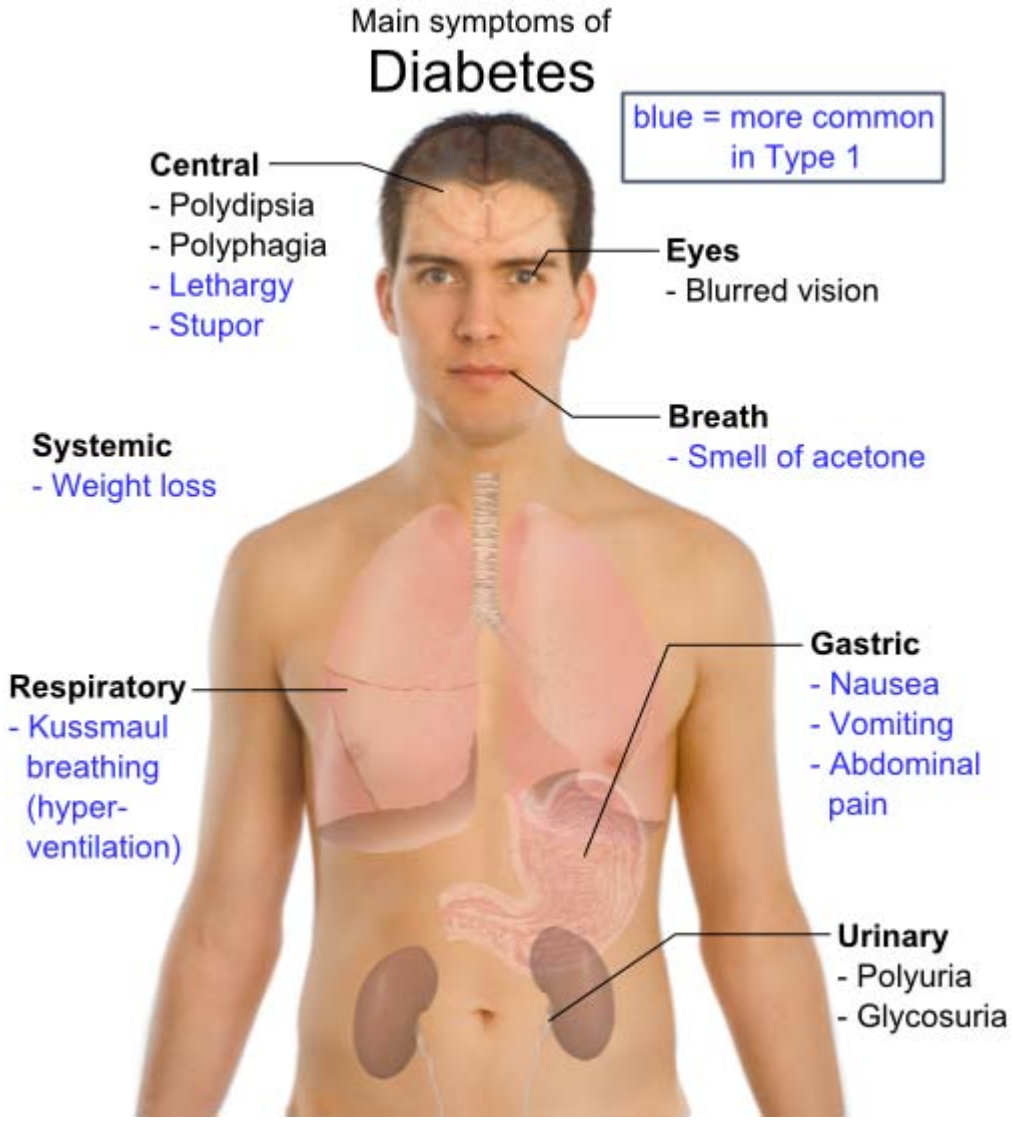
Latent autoimmune diabetes of adults is a condition in which Type 1 diabetes develops in adults. Adults with LADA are frequently initially misdiagnosed as having Type 2 diabetes, based on age rather than etiology.

Some cases of diabetes are caused by the body's tissue receptors not responding to insulin (even when insulin levels are normal, which is what separates it from type 2 diabetes); this form is very uncommon. Genetic mutations (autosomal or mitochondrial) can lead to defects in beta cell function. Abnormal insulin action may also have been genetically determined in some cases. Any disease that causes extensive damage to the pancreas may lead to diabetes (for example, chronic pancreatitis and cystic fibrosis). Diseases associated with excessive secretion of insulin-antagonistic hormones can cause diabetes (which is typically resolved once the hormone excess is removed). Many drugs impair insulin secretion and some toxins damage pancreatic beta cells. The ICD-10 (1992) diagnostic entity, *malnutrition-related diabetes mellitus* (MRDM or MMDM, ICD-10 code E12), was deprecated by the World Health Organization when the current taxonomy was introduced in 1999.

Following is a comprehensive list of other causes of diabetes:

- Genetic defects of β-cell Function
  - Maturity onset diabetes of the young (MODY)
  - Mitochondrial DNA mutations
- Genetic defects in insulin processing or insulin action
  - Defects in proinsulin conversion
  - Insulin gene mutations
  - Insulin receptor mutations
- Exocrine Pancreatic Defects
  - Chronic pancreatitis
  - Pancreatectomy
  - Pancreatic neoplasia
  - Cystic fibrosis
  - Hemochromatosis
  - Fibrocalculous pancreatopathy
- Endocrinopathies
  - Growth hormone excess (acromegaly)
  - Cushing syndrome
  - Hyperthyroidism
  - Pheochromocytoma
  - Glucagonoma
- Infections
  - Cytomegalovirus infection
  - Coxsackievirus B
- Drugs
  - Glucocorticoids
  - Thyroid hormone
  - β-adrenergic agonists

Signs and symptoms



Overview of the most significant symptoms of diabetes

The classical symptoms of diabetes are polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger). Symptoms may develop rapidly (weeks or months) in type 1 diabetes while in type 2 diabetes they usually develop much more slowly and may be subtle or absent.

Prolonged high blood glucose causes glucose absorption, which leads to changes in the shape of the lenses of the eyes, resulting in vision changes; sustained sensible glucose control usually returns the lens to its original shape. Blurred vision is a common complaint leading to a diabetes diagnosis; type 1 should always be suspected in cases of rapid vision change, whereas with type 2 change is generally more gradual, but should still be suspected.

People (usually with type 1 diabetes) may also present with diabetic ketoacidosis, a state of metabolic dysregulation characterized by the smell of acetone; a rapid, deep breathing known as Kussmaul breathing; nausea; vomiting and abdominal pain; and an altered states of consciousness.

A rarer but equally severe possibility is hyperosmolar nonketotic state, which is more common in type 2 diabetes and is mainly the result of dehydration. Often, the patient has been drinking extreme amounts of sugar-containing drinks, leading to a vicious circle in regard to the water loss.

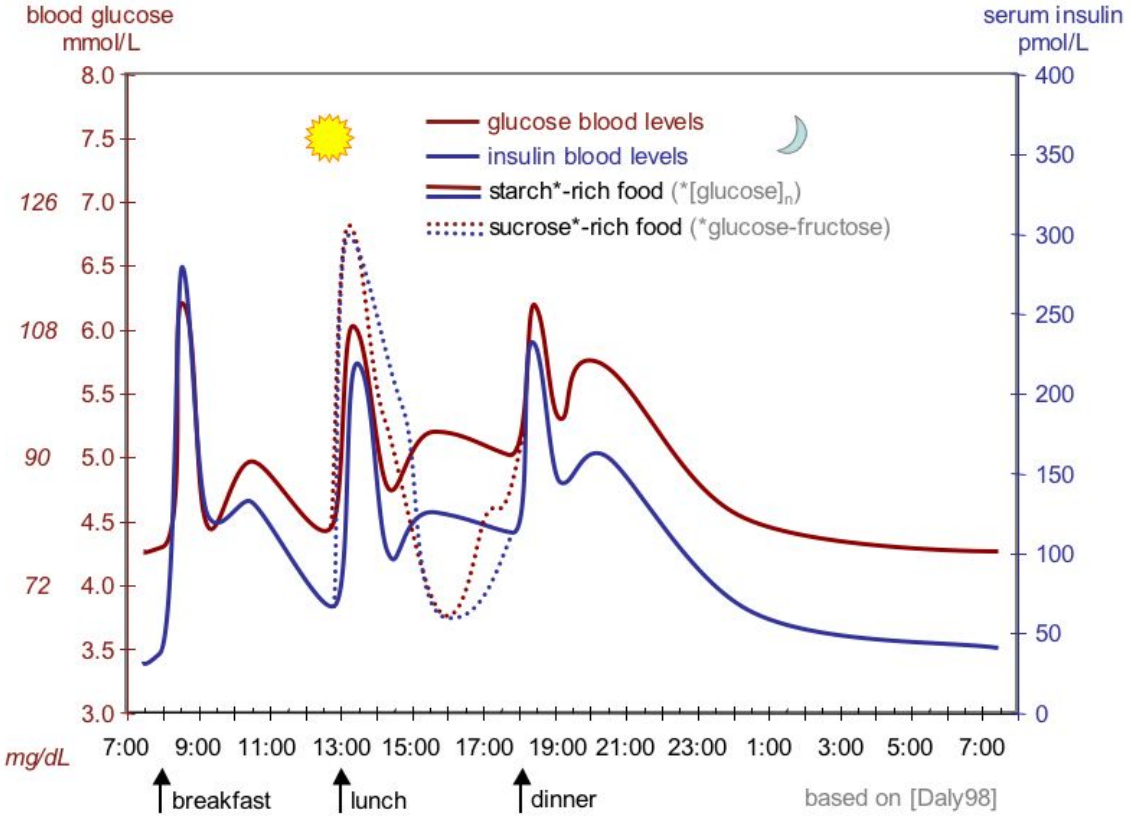
A number of skin rashes can occur in diabetes that are collectively known as diabetic dermadromes.

Causes

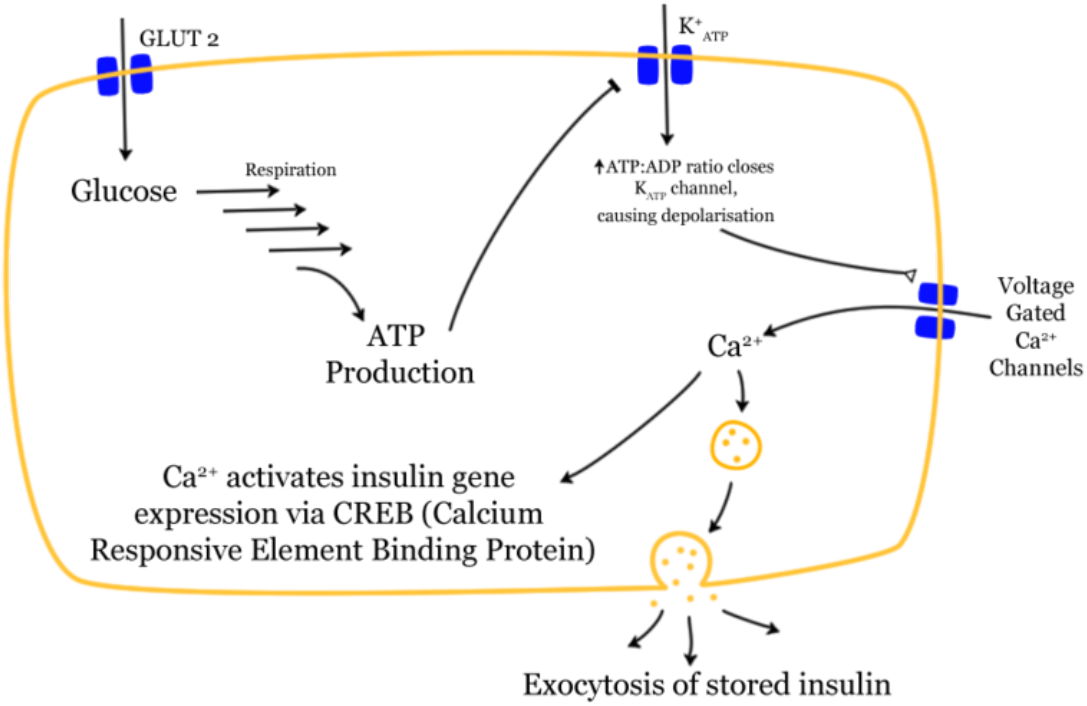
The cause of diabetes depends on the type. Type 2 diabetes is due primarily to lifestyle factors and genetics.

Type 1 diabetes is also partly inherited and then triggered by certain infections, with some evidence pointing at Coxsackie B4 virus. There is a genetic element in individual susceptibility to some of these triggers which has been traced to particular HLA genotypes (i.e., the genetic "self" identifiers relied upon by the immune system). However, even in those who have inherited the susceptibility, type 1 diabetes mellitus seems to require an environmental trigger.

Pathophysiology



The fluctuation of blood sugar (red) and the sugar-lowering hormone insulin (blue) in humans during the course of a day with three meals. One of the effects of a sugar-rich vs a starch-rich meal is highlighted.



Mechanism of insulin release in normal pancreatic beta cells. Insulin production is more or less constant within the beta cells, irrespective of blood glucose levels. It is stored within vacuoles pending release, via exocytosis, which is primarily triggered by food, chiefly food containing absorbable glucose. The chief trigger is a rise in blood glucose levels after eating

Insulin is the principal hormone that regulates uptake of glucose from the blood into most cells (primarily muscle and fat cells, but not central nervous system cells). Therefore deficiency of insulin or the insensitivity of its receptors plays a central role in all forms of diabetes mellitus.

Humans are capable of digesting some carbohydrates, in particular those most common in food; starch, and some disaccharides such as sucrose, are converted within a few hours to simpler forms most notably the monosaccharide glucose, the principal carbohydrate energy source used by the body. The rest are passed on for processing by gut flora largely in the colon. Insulin is released into the blood by beta cells (β-cells), found in the Islets of Langerhans in the pancreas, in response to rising levels of blood glucose, typically after eating. Insulin is used by about two-thirds of the body's cells to absorb glucose from the blood for use as fuel, for conversion to other needed molecules, or for storage.

Insulin is also the principal control signal for conversion of glucose to glycogen for internal storage in liver and muscle cells. Lowered glucose levels result both in the reduced release of insulin from the beta cells and in the reverse conversion of glycogen to glucose when glucose levels fall. This is mainly controlled by the hormone glucagon which acts in the opposite manner to insulin. Glucose thus forcibly produced from

internal liver cell stores (as glycogen) re-enters the bloodstream; muscle cells lack the necessary export mechanism. Normally liver cells do this when the level of insulin is low (which normally correlates with low levels of blood glucose).

Higher insulin levels increase some anabolic ("building up") processes such as cell growth and duplication, protein synthesis, and fat storage. Insulin (or its lack) is the principal signal in converting many of the bidirectional processes of metabolism from a catabolic to an anabolic direction, and vice versa. In particular, a low insulin level is the trigger for entering or leaving ketosis (the fat burning metabolic phase).

If the amount of insulin available is insufficient, if cells respond poorly to the effects of insulin (insulin insensitivity or resistance), or if the insulin itself is defective, then glucose will not have its usual effect so that glucose will not be absorbed properly by those body cells that require it nor will it be stored appropriately in the liver and muscles. The net effect is persistent high levels of blood glucose, poor protein synthesis, and other metabolic derangements, such as acidosis.

When the glucose concentration in the blood is raised beyond its renal threshold (about 10 mmol/L, although this may be altered in certain conditions, such as pregnancy), reabsorption of glucose in the proximal renal tubuli is incomplete, and part of the glucose remains in the urine (glycosuria). This increases the osmotic pressure of the urine and inhibits reabsorption of water by the kidney, resulting in increased urine production (polyuria) and increased fluid loss. Lost blood volume will be replaced osmotically from water held in body cells and other body compartments, causing dehydration and increased thirst.

Diagnosis

2006 WHO Diabetes criteria

Condition	**2 hour glucose**	**Fasting glucose**
	mmol/l(mg/dl)	mmol/l(mg/dl)
Normal	<7.8 (<140)	<6.1 (<110)
Impaired fasting glycaemia	<7.8 (<140)	≥ 6.1(≥110) & <7.0(<126)
Impaired glucose tolerance	≥7.8 (≥140)	<7.0 (<126)
Diabetes mellitus	≥11.1 (≥200)	≥7.0 (≥126)

Diabetes mellitus is characterized by recurrent or persistent hyperglycemia, and is diagnosed by demonstrating any one of the following:

- Fasting plasma glucose level ≥ 7.0 mmol/L (126 mg/dL).
- Plasma glucose ≥ 11.1 mmol/L (200 mg/dL) two hours after a 75 g oral glucose load as in a glucose tolerance test.
- Symptoms of hyperglycemia and casual plasma glucose ≥ 11.1 mmol/L (200 mg/dL).
- Glycated hemoglobin (Hb A1C) ≥ 6.5%.

A positive result, in the absence of unequivocal hyperglycemia, should be confirmed by a repeat of any of the above-listed methods on a different day. It is preferable to measure a fasting glucose level because of the ease of measurement and the considerable time commitment of formal glucose tolerance testing, which takes two hours to complete and offers no prognostic advantage over the fasting test. According to the current definition, two fasting glucose measurements above 126 mg/dL (7.0 mmol/L) is considered diagnostic for diabetes mellitus.

People with fasting glucose levels from 100 to 125 mg/dL (5.6 to 6.9 mmol/L) are considered to have impaired fasting glucose. Patients with plasma glucose at or above 140 mg/dL (7.8 mmol/L), but not over 200 mg/dL (11.1 mmol/L), two hours after a 75 g oral glucose load are considered to have impaired glucose tolerance. Of these two pre-diabetic states, the latter in particular is a major risk factor for progression to full-blown diabetes mellitus as well as cardiovascular disease.

Management

Diabetes mellitus is a chronic disease which is difficult to cure. Management concentrates on keeping blood sugar levels as close to normal ("euglycemia") as possible without presenting undue patient danger. This can usually be with close dietary management, exercise, and use of appropriate medications (insulin only in the case of type 1 diabetes mellitus. Oral medications may be used in the case of type 2 diabetes, as well as insulin).

Patient education, understanding, and participation is vital since the complications of diabetes are far less common and less severe in people who have well-managed blood sugar levels. Wider health problems may accelerate the deleterious effects of diabetes. These include smoking, elevated cholesterol levels, obesity, high blood pressure, and lack of regular exercise.

Lifestyle modifications

There are roles for patient education, dietetic support, sensible exercise, with the goal of keeping both short-term and long-term blood glucose levels within acceptable bounds. In addition, given the associated higher risks of cardiovascular disease, lifestyle modifications are recommended to control blood pressure.

Medications

Oral medications

Routine use of aspirin has not been found to improve outcomes in uncomplicated diabetes.

Insulin

Type 1 treatments usually include combinations of regular or NPH insulin, and/or synthetic insulin analogs.

Support

In countries using a general practitioner system, such as the United Kingdom, care may take place mainly outside hospitals, with hospital-based specialist care used only in case of complications, difficult blood sugar control, or research projects. In other circumstances, general practitioners and specialists share care of a patient in a team approach. Optometrists, podiatrists/chiropodists, dietitians, physiotherapists, nursing specialists (e.g., DSNs (Diabetic Specialist Nurse)), nurse practitioners, or Certified Diabetes Educators, may jointly provide multidisciplinary expertise. In countries where patients must provide for their own health care (e.g. in the US, and in much of the undeveloped world).

Peer support links people living with diabetes. Within peer support, people with a common illness share knowledge and experience that others, including many health workers, do not have. Peer support is frequent, ongoing, accessible and flexible and can take many forms—phone calls, text messaging, group meetings, home visits, and even grocery shopping. It complements and enhances other health care services by creating the emotional, social and practical assistance necessary for managing disease and staying healthy.

Prognosis

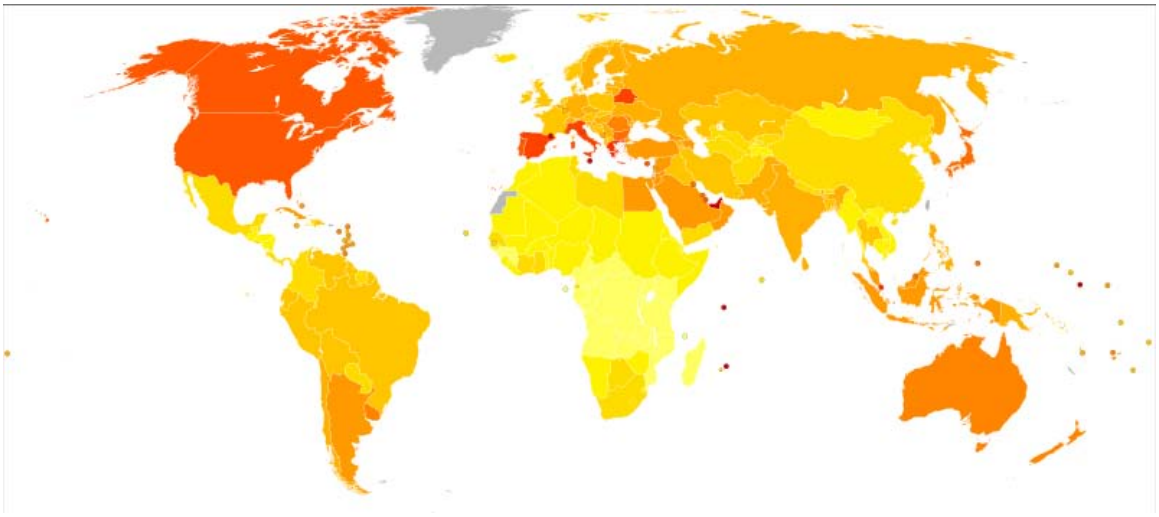
Diabetes doubles the risk of vascular problems, including cardiovascular disease.

According to one study, women with high blood pressure (hypertension) were three times more likely to develop type 2 diabetes as compared with women with optimal BP after adjusting for various factors such as age, ethnicity, smoking, alcohol intake, body mass index (BMI), exercise, family history of diabetes, etc. The study was conducted by researchers from the Brigham and Women's Hospital, Harvard Medical School and the Harvard School of Public Health, USA, who followed over 38,000 female health professionals for ten years.

Except in the case of type 1 diabetes, which always requires insulin replacement, the way type 2 diabetes is managed may change with age. Insulin production decreases because of age-related impairment of pancreatic beta cells. Additionally, insulin resistance increases because of the loss of lean tissue and the accumulation of fat, particularly intra-abdominal fat, and the decreased tissue sensitivity to insulin. Glucose tolerance progressively declines with age, leading to a high prevalence of type 2 diabetes and postchallenge hyperglycemia in the older population. Age-related glucose intolerance in humans is often accompanied by insulin resistance, but circulating insulin levels are similar to those of younger people. Treatment goals for older patients with diabetes vary with the

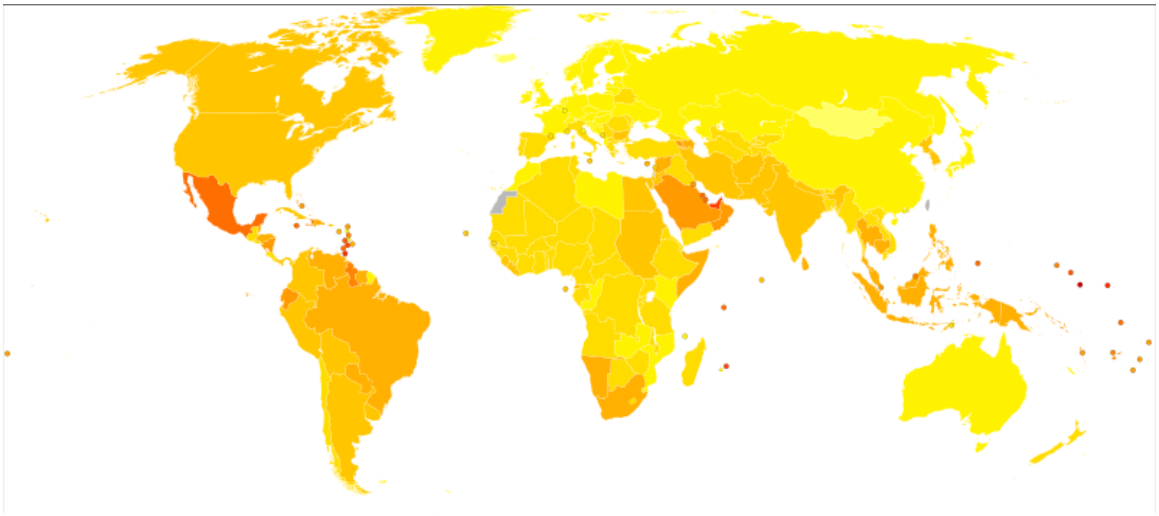
individual, and take into account health status, as well as life expectancy, level of dependence, and willingness to adhere to a treatment regimen. Glycated hemoglobin is better than fasting glucose for determining risks of cardiovascular disease and death from any cause.

Epidemiology



Prevalence of diabetes worldwide in 2000 (per 1000 inhabitants). World average was 2.8%.

- no data
- ≤ 7.5
- 7.5–15
- 15–22.5
- 22.5–30
- 30–37.5
- 37.5–45
- 45–52.5
- 52.5–60
- 60–67.5
- 67.5–75
- 75–82.5
- ≥ 82.5



Disability-adjusted life year for diabetes mellitus per 100,000 inhabitants in 2002.
no data
≤ 100
100-200
200-300
300-400
400-500
500-600
600-700
700-800
800-900
900-1000
1000-1500
≥ 1500

In 2000, according to the World Health Organization, at least 171 million people worldwide suffer from diabetes, or 2.8% of the population. Its incidence is increasing rapidly, and it is estimated that by 2030, this number will almost double. Diabetes mellitus occurs throughout the world, but is more common (especially type 2) in the more developed countries. The greatest increase in prevalence is, however, expected to occur in Asia and Africa, where most patients will probably be found by 2030. The increase in incidence of diabetes in developing countries follows the trend of urbanization and lifestyle changes, perhaps most importantly a "Western-style" diet. This has suggested an environmental (i.e., dietary) effect, but there is little understanding of the mechanism(s) at present, though there is much speculation, some of it most compellingly presented.

For at least 20 years, diabetes rates in North America have been increasing substantially. In 2010 nearly 26 million people have diabetes in the United States alone, from those 7 million people remain undiagnosed. Other 57 million people are estimated to have pre-diabetes.

The Centers for Disease Control has termed the change an epidemic. The National Diabetes Information Clearinghouse estimates that diabetes costs $132 billion in the United States alone every year. About 5%–10% of diabetes cases in North America are type 1, with the rest being type 2. The fraction of type 1 in other parts of the world differs. Most of this difference is not currently understood. The American Diabetes Association cite the 2003 assessment of the National Center for Chronic Disease Prevention and Health Promotion (Centers for Disease Control and Prevention) that 1 in 3 Americans born after 2000 will develop diabetes in their lifetime.

According to the American Diabetes Association, approximately 18.3% (8.6 million) of Americans age 60 and older have diabetes. Diabetes mellitus prevalence increases with age, and the numbers of older persons with diabetes are expected to grow as the elderly population increases in number. The National Health and Nutrition Examination Survey (NHANES III) demonstrated that, in the population over 65 years old, 18% to 20% have diabetes, with 40% having either diabetes or its precursor form of impaired glucose tolerance.

Indigenous populations in first world countries have a higher prevalence and increasing incidence of diabetes than their corresponding non-indigenous populations. In Australia the age-standardised prevalence of self-reported diabetes in Indigenous Australians is almost 4 times that of non-indigenous Australians. Preventative community health programs such as Sugar Man (diabetes education) are showing some success in tackling this problem.

History

The term *diabetes* (Greek: διαβήτης, *diabētēs*) was coined by Aretaeus of Cappadocia. It was derived from the Greek verb διαβαίνειν, *diabaínein*, itself formed from the prefix *dia*-, "across, apart," and the verb *bainein*, "to walk, stand." The verb *diabeinein* meant "to stride, walk, or stand with legs asunder"; hence, its derivative *diabētēs* meant "one that straddles," or specifically "a compass, siphon." The sense "siphon" gave rise to the use of *diabētēs* as the name for a disease involving the discharge of excessive amounts of urine. Diabetes is first recorded in English, in the form diabete, in a medical text written around 1425. In 1675, Thomas Willis added the word *mellitus*, from the Latin meaning "honey", a reference to the sweet taste of the urine. This sweet taste had been noticed in urine by the ancient Greeks, Chinese, Egyptians, Indians, and Persians. In 1776, Matthew Dobson confirmed that the sweet taste was because of an excess of a kind of sugar in the urine and blood of people with diabetes.

Diabetes mellitus appears to have been a death sentence in the ancient era. Hippocrates makes no mention of it, which may indicate that he felt the disease was incurable. Aretaeus did attempt to treat it but could not give a good prognosis; he commented that "life (with diabetes) is short, disgusting and painful."

Sushruta (6th century BCE) identified diabetes and classified it as *Medhumeha*. He further identified it with obesity and sedentary lifestyle, advising exercises to help "cure"

it. The ancient Indians tested for diabetes by observing whether ants were attracted to a person's urine, and called the ailment "sweet urine disease" (Madhumeha). The Chinese, Japanese and Korean words for diabetes are based on the same ideographs (糖尿病) which mean "sugar urine disease".

In medieval Persia, Avicenna (980–1037) provided a detailed account on diabetes mellitus in *The Canon of Medicine*, "describing the abnormal appetite and the collapse of sexual functions," and he documented the sweet taste of diabetic urine. Like Aretaeus before him, Avicenna recognized a primary and secondary diabetes. He also described diabetic gangrene, and treated diabetes using a mixture of lupine, trigonella (fenugreek), and zedoary seed, which produces a considerable reduction in the excretion of sugar, a treatment which is still prescribed in modern times. Avicenna also "described diabetes insipidus very precisely for the first time", though it was later Johann Peter Frank (1745–1821) who first differentiated between diabetes mellitus and diabetes insipidus.

Although diabetes has been recognized since antiquity, and treatments of various efficacy have been known in various regions since the Middle Ages, and in legend for much longer, pathogenesis of diabetes has only been understood experimentally since about 1900. The discovery of a role for the pancreas in diabetes is generally ascribed to Joseph von Mering and Oskar Minkowski, who in 1889 found that dogs whose pancreas was removed developed all the signs and symptoms of diabetes and died shortly afterwards. In 1910, Sir Edward Albert Sharpey-Schafer suggested that people with diabetes were deficient in a single chemical that was normally produced by the pancreas—he proposed calling this substance *insulin*, from the Latin *insula*, meaning island, in reference to the insulin-producing islets of Langerhans in the pancreas.

The endocrine role of the pancreas in metabolism, and indeed the existence of insulin, was not further clarified until 1921, when Sir Frederick Grant Banting and Charles Herbert Best repeated the work of Von Mering and Minkowski, and went further to demonstrate they could reverse induced diabetes in dogs by giving them an extract from the pancreatic islets of Langerhans of healthy dogs. Banting, Best, and colleagues (especially the chemist Collip) went on to purify the hormone insulin from bovine pancreases at the University of Toronto. This led to the availability of an effective treatment—insulin injections—and the first patient was treated in 1922. For this, Banting and laboratory director MacLeod received the Nobel Prize in Physiology or Medicine in 1923; both shared their Prize money with others in the team who were not recognized, in particular Best and Collip. Banting and Best made the patent available without charge and did not attempt to control commercial production. Insulin production and therapy rapidly spread around the world, largely as a result of this decision. Banting is honored by World Diabetes Day which is held on his birthday, November 14.

The distinction between what is now known as type 1 diabetes and type 2 diabetes was first clearly made by Sir Harold Percival (Harry) Himsworth, and published in January 1936.

Despite the availability of treatment, diabetes has remained a major cause of death. For instance, statistics reveal that the cause-specific mortality rate during 1927 amounted to about 47.7 per 100,000 population in Malta.

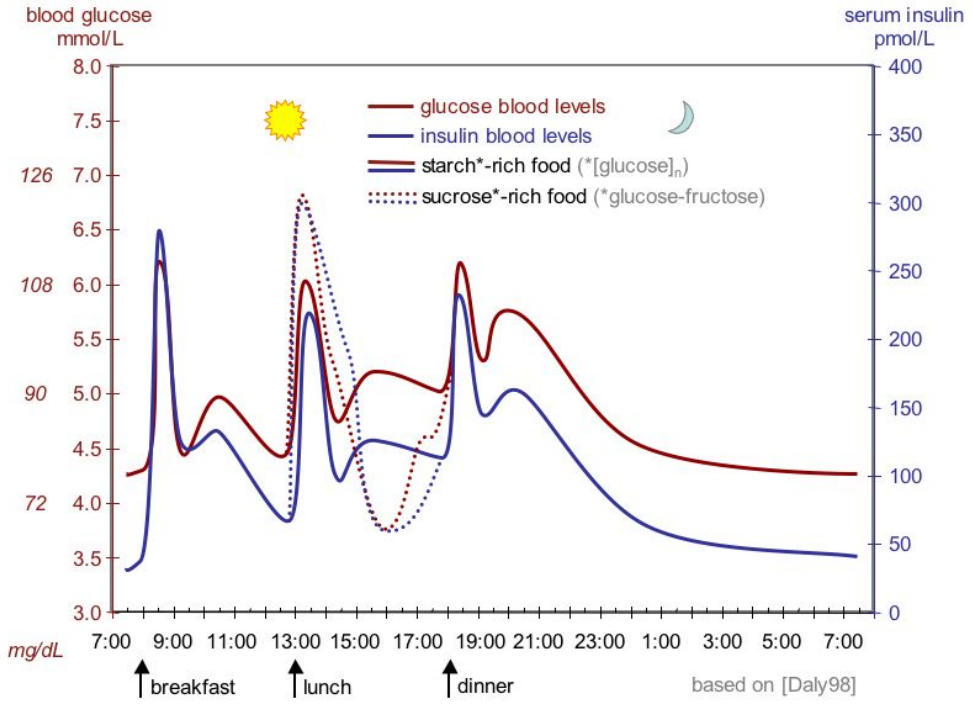
Other landmark discoveries include:

- Identification of the first of the sulfonylureas in 1942
- Reintroduction of the use of biguanides for Type 2 diabetes in the late 1950s. The initial phenformin was withdrawn worldwide (in the U.S. in 1977) due to its potential for sometimes fatal lactic acidosis and metformin was first marketed in France in 1979, but not until 1994 in the US.
- The determination of the amino acid sequence of insulin (by Sir Frederick Sanger, for which he received a Nobel Prize)
- The radioimmunoassay for insulin, as discovered by Rosalyn Yalow and Solomon Berson (gaining Yalow the 1977 Nobel Prize in Physiology or Medicine)
- The three-dimensional structure of insulin (PDB 2INS)
- Dr Gerald Reaven's identification of the constellation of symptoms now called metabolic syndrome in 1988
- Demonstration that intensive glycemic control in type 1 diabetes reduces chronic side effects more as glucose levels approach 'normal' in a large longitudinal study, and also in type 2 diabetics in other large studies
- Identification of the first thiazolidinedione as an effective insulin sensitizer during the 1990s

In 1980, U.S. biotech company Genentech developed human insulin. The insulin is isolated from genetically altered bacteria (the bacteria contain the human gene for synthesizing human insulin), which produce large quantities of insulin. The purified insulin is distributed to pharmacies for use by diabetes patients.

Chapter 2

Blood Sugar



The fluctuation of blood sugar (red) and the sugar-lowering hormone insulin (blue) in humans during the course of a day with three meals. One of the effects of a sugar-rich vs a starch-rich meal is highlighted.

The **blood sugar concentration** or **blood glucose level** is the amount of glucose (sugar) present in the blood of a human or animal. Normally in mammals, the body maintains the blood glucose level at a reference range between about 3.6 and 5.8 mM (mmol/L, i.e., millimoles/liter) (64.8 and 104.4 mg/dL). The human body naturally tightly regulates blood glucose levels as a part of metabolic homeostasis.

Glucose is the primary source of energy for the body's cells, and blood lipids (in the form of fats and oils) are primarily a compact energy store. Glucose is transported from the intestines or liver to body cells via the bloodstream, and is made available for cell absorption via the hormone insulin, produced by the body primarily in the pancreas.

The mean normal blood glucose level in humans is about 4 mM (4 mmol/L or 72 mg/dL, i.e. milligrams/deciliter); however, this level fluctuates throughout the day. Glucose levels are usually lowest in the morning, before the first meal of the day (termed "the fasting level"), and rise after meals for an hour or two by a few milliMolar.

Blood sugar levels outside the normal range may be an indicator of a medical condition; . A persistently high level is referred to as hyperglycemia; low levels are referred to as hypoglycemia. Diabetes mellitus is characterized by persistent hyperglycemia from any of several causes, and is the most prominent disease related to failure of blood sugar regulation. A temporarily elevated blood sugar level may also result from severe stress, such as trauma, stroke, myocardial infarction, surgery, or illness. Intake of alcohol causes an initial surge in blood sugar, and later tends to cause levels to fall. Also, certain drugs can increase or decrease glucose levels.

Blood glucose measurement units

The international standard way of measuring blood glucose levels are in terms of a molar concentration, measured in mmol/L (millimoles per litre; or millimolar, abbreviated mM). In the United States, mass concentration is measured in mg/dL (milligrams per decilitre).

Since the molecular weight of glucose $C_6H_{12}O_6$ is about 1680 g/mol, for the measurement of glucose, the difference between the two scales is a factor of 17, so that 1 mmol/L of glucose is equivalent to 18 mg/dL.

Normal values

Many factors affect a person's blood sugar level. A body's homeostatic mechanism, when operating normally, restores the blood sugar level to a narrow range of about 82 to 110 mg/dL (4.4 to 6.1 mmol/L). (These levels are in contradiction with the levels cited at the beginning, though the latter are quoted for mammals in general).

Despite widely variable intervals between meals or the occasional consumption of meals with a substantial carbohydrate load, human blood glucose levels normally remain within the normal range. However, shortly after eating, the blood glucose level may rise temporarily up to 140 mg/dL (7.8 mmol/L) or a bit more in non-diabetics. The American Diabetes Association recommends a post-meal glucose level of less than 180 mg/dl (10 mmol/L) and a pre-meal plasma glucose of 90–130 mg/dL (5 to 7.2 mmol/L).

The actual amount of glucose in the blood and body fluids is very small. The control mechanism in the human body works on very small quantities of glucose. In a healthy adult male of 165 lb (75 kg) with a blood volume of 1.3 gal (5 litres), a blood glucose level of 100 mg/dL or 5.5 mmol/L corresponds to about 5 g (0.2 oz or 0.002 gal, 1/500 of the total) of glucose in the blood and approximately 45 g (1½ ounces) in the total body water (which includes more than merely blood and will be usually about 60% of the total

body weight in men). (Small sugar packets provided in many restaurants with coffee or tea are about 2.8 grams each.)

Regulation

The body's homeostatic mechanism keeps blood glucose levels within a narrow range. It is composed of several interacting systems, of which hormone regulation is the most important.

There are two types of mutually antagonistic metabolic hormones affecting blood glucose levels:

- catabolic hormones (such as glucagon, cortisol and catecholamines) which increase blood glucose;
- and one anabolic hormone (insulin), which decreases blood glucose.

Health effects

If blood sugar levels drop too low, a potentially fatal condition called hypoglycemia develops. Symptoms may include lethargy, impaired mental functioning; irritability; shaking, twitching, weakness in arm and leg muscles; pale complexion; sweating; paranoid or aggressive mentality and loss of consciousness. Brain damage is even possible.

If levels remain too high, appetite is suppressed over the short term. Long-term hyperglycemia causes many of the long-term health problems associated with diabetes, including eye, kidney, heart disease and nerve damage.

Low blood sugar

Mechanisms that restore satisfactory blood glucose levels after hypoglycemia must be quick and effective to prevent extremely serious consequences of insufficient glucose: confusion or unsteadiness and, in the extreme, coma. It is far more dangerous to have too little glucose in the blood than too much, at least temporarily. In healthy individuals, blood glucose-regulating mechanisms are generally quite effective, and symptomatic hypoglycemia is generally found only in diabetics using insulin or other pharmacological treatment. Hypoglycemic episodes can vary greatly between persons and from time to time, both in severity and swiftness of onset. For severe cases, prompt medical assistance is essential, as damage to brain and other tissues and even death will result from sufficiently low blood-glucose levels.

Some healthy individuals report drowsiness or impaired cognitive function several hours after meals, symptoms which they believe are related to a drop in blood sugar, or low blood sugar.

Glucose measurement

Sample type

Glucose is measured in whole blood, plasma or serum. Historically, blood glucose values were given in terms of whole blood, but most laboratories now measure and report the serum glucose levels. Because red blood cells (erythrocytes) have a higher concentration of protein (e.g., hemoglobin) than serum, serum has a higher water content and consequently more dissolved glucose than does whole blood. To convert from whole-blood glucose, multiplication by 1.15 has been shown to generally give the serum/plasma level.

Collection of blood in clot tubes for serum chemistry analysis permits the metabolism of glucose in the sample by blood cells until separated by centrifugation. Red blood cells, for instance, do not require insulin to intake glucose from the blood. Higher than normal amounts of white or red blood cell counts can lead to excessive glycolysis in the sample, with substantial reduction of glucose level if the sample is not processed quickly. Ambient temperature at which the blood sample is kept prior to centrifuging and separation of plasma/serum also affects glucose levels. At refrigerator temperatures, glucose remains relatively stable for several hours in a blood sample. At room temperature (25 °C), a loss of 7–10 mg/dL (or 0.4 mmol/L) of total glucose per hour should be expected in whole blood samples. Loss of glucose under these conditions can be prevented by using Fluoride tubes (i.e., gray-top) since fluoride inhibits glycolysis. However, these should only be used when blood will be transported from one hospital laboratory to another for glucose measurement. Red-top serum separator tubes also preserve glucose in samples after being centrifuged isolating the serum from cells.

To prevent contamination of the sample with intravenous fluids, particular care should be given to drawing blood samples from the arm opposite the one in which an intravenous line is inserted. Alternatively, blood can be drawn from the same arm with an IV line after the IV has been turned off for at least 5 minutes, and the arm has been elevated to drain infused fluids away from the vein. Inattention can lead to large errors, since as little as 10% contamination with a 5% glucose solution (D5W) will elevate glucose in a sample by 500 mg/dl or more. Remember that the actual concentration of glucose in blood is very low, even in the hyperglycemic.

Arterial, capillary and venous blood have comparable glucose levels in a fasting individual. Following meals, venous levels are somewhat lower than those in capillary or arterial blood; a common estimate is about 10%.

Measurement techniques

Two major methods have been used to measure glucose. The first, still in use in some places, is a chemical method exploiting the *nonspecific reducing* property of glucose in a reaction with an indicator substance that changes color when reduced. Since other blood compounds also have reducing properties (e.g., urea, which can be abnormally high in

uremic patients), this technique can produce erroneous readings in some situations (5 to 15 mg/dl has been reported). The more recent technique, using enzymes specific to glucose, is less susceptible to this kind of error. The two most common employed enzymes are glucose oxidase and hexokinase.

In either case, the chemical system is commonly contained on a test strip which is inserted into a meter, and then has a blood sample applied. Test-strip shapes and their exact chemical composition vary between meter systems and cannot be interchanged. Formerly, some test strips were read (after timing and wiping away the blood sample) by visual comparison against a color chart printed on the vial label. Strips of this type are still used for urine glucose readings, but for blood glucose levels they are obsolete. Their error rates were, in any case, much higher.

Urine glucose readings, however taken, are much less useful. In properly functioning kidneys, glucose does not appear in urine until the renal threshold for glucose has been exceeded. This is substantially above any normal glucose level, and is evidence of an existing severe hyperglycemic condition. However, as urine is stored in the bladder, any glucose in it might have been produced at any time since the last time the bladder was emptied. Since metabolic conditions change rapidly, as a result of any of several factors, this is delayed news and gives no warning of a developing condition. Blood glucose monitoring is far preferable, both clinically and for home monitoring by patients.

I. CHEMICAL METHODS		
A. Oxidation-reduction reaction		
$\text{Glucose} + \text{Alkaline copper tartarate} \xrightarrow{\text{Reduction}} \text{Cuprous oxide}$		
1. Alkaline copper reduction		
Folin-Wu method	$Cu^{++} + \text{Phosphomolybdic acid} \xrightarrow{\text{Oxidation}} \text{Phosphomolybdenum oxide}$	Blue end-product
Benedict's method	• Modification of Folin-Wu method for qualitative urine glucose	
Nelson-Somogyi method	$Cu^{++} + \text{Arsenomolybdic acid} \xrightarrow{\text{Oxidation}} \text{Arsenomolybdenum oxide}$	Blue end-product
Neocuproine method	$Cu^{++} + \text{Neocuproine} \xrightarrow{\text{Oxidation}} Cu^{++}\text{neocuproine complex}_{*}$	Yellow-orange color neocuproine
Shaeffer-Hartmann-Somogyi	• Uses the principle of iodine reaction with cuprous byproduct. • Excess I_2 is then titrated with thiosulfate.	
2. Alkaline Ferricyanide Reduction		

Hagedorn-Jensen	$\text{Glucose} + \text{Alkaline ferricyanide} \longrightarrow \text{Ferrocyanide}$	Colorless end product; other reducing substances interfere with reaction
B. Condensation		
Ortho-toluidine method	• Uses aromatic amines and hot acetic acid • Forms Glycosylamine and Schiff's base which is emerald green in color • This is the most specific method, but the reagent used is toxic	
Anthrone (phenols) method	• Forms hydroxymethyl furfural in hot acetic acid	
II. ENZYMATIC METHODS		
A. Glucose oxidase		
	$\text{Glucose} + O_2 \xrightarrow[\text{Oxidation}]{\text{glucose oxidase}} \text{Cuprous oxide}$	
Saifer–Gerstenfeld method	$H_2O_2 + \textit{O}\text{-dianisidine} \xrightarrow[\text{Oxidation}]{\text{peroxidase}} H_2O + \text{oxidized chromogen}$	Inhibited by reducing substances like BUA, bilirubin, glutathione, ascorbic acid
Trinder method	• uses 4-aminophenazone oxidatively coupled with phenol • Subject to less interference by increases serum levels of creatinine, uric acid or hemoglobin • Inhibited by catalase	
Kodak Ektachem	• A dry chemistry method • Uses reflectance spectrophotometry to measure the intensity of color through a lower transparent film	
Glucometer	• Home monitoring blood glucose assay method • Uses a strip impregnated with a glucose oxidase reagent	
B. Hexokinase		
	$\text{Glucose} + \text{ATP} \xrightarrow[\text{Phosphorylation}]{\text{Hexokinase}+Mg^{++}} \text{G-6PO}_4 + \text{ADP}$ $\text{G-6PO}_4 + \text{NADP} \xrightarrow[\text{Oxidation}]{\text{G-6PD}} \text{G-Phosphogluconate} + \text{NADPH} + H^+$	
	• NADP as cofactor • NADPH (reduced product) is measured in 340 nm • More specific than glucose oxidase method due to $G\text{-}6PO_4$, which inhibits interfering substances except when sample is hemolyzed	

Blood glucose laboratory tests

1. fasting blood sugar (i.e., glucose) test (FBS)
2. urine glucose test
3. two-hr postprandial blood sugar test (2-h PPBS)
4. oral glucose tolerance test (OGTT)
5. intravenous glucose tolerance test (IVGTT)
6. glycosylated hemoglobin (HbA_{1C})
7. self-monitoring of glucose level via patient testing

Clinical correlation

The fasting blood glucose level, which is measured after a fast of 8 hours, is the most commonly used indication of overall glucose homeostasis, largely because disturbing events such as food intake are avoided. Conditions affecting glucose levels are shown in the table below. Abnormalities in these test results are due to problems in the multiple control mechanism of glucose regulation.

The metabolic response to a carbohydrate challenge is conveniently assessed by a postprandial glucose level drawn 2 hours after a meal or a glucose load. In addition, the glucose tolerance test, consisting of several timed measurements after a standardized amount of oral glucose intake, is used to aid in the diagnosis of diabetes. It is regarded as the gold standard of clinical tests of the insulin / glucose control system, but is difficult to administer, requiring much time and repeated blood tests. In comparison, the fasting blood glucose level is a much poorer screening test because of the high variability of the experimental conditions such as the carbohydrate content of the last meal and the energy expenditure between the last meal and the measurement. Actually, many people with prediabetes or diabetes can have a fasting blood glucose below the prediabetic/diabetic threshold if their last meal happened to be low in carbohydrate and they burnt all the related glucose in their blood stream before taking the test. Note that food commonly includes carbohydrates which don't participate in the metabolic control system; simple sugars such as fructose, many of the disaccarhides (which either contain simple sugars other than glucose or cannot be digested by humans) and the more complex sugars which also cannot be digested by humans. And there are carbohydrates which are not digested even with the assistance of gut bacteria; several of the fibres (soluble or insoluble) are chemically carbohydrates. Food also commonly contains components which affect glucose (and other sugar's) digestion; fat, for example slows down digestive processing, even for such easily handled food constituents as starch. Avoiding the effects of food on blood glucose measurement is important for reliable results since those effects are so variable.

Error rates for blood glucose measurements systems vary, depending on laboratories, and on the methods used. Colorimetry techniques can be biased by color changes in test strips (from airborne or finger borne contamination, perhaps) or interference (e.g., tinting contaminants) with light source or the light sensor. Electrical techniques are less susceptible to these errors, though not to others. In home use, the most important issue is

not accuracy, but trend. Thus if a meter / test strip system is consistently wrong by 10%, there will be little consequence, as long as changes (e.g., due to exercise or medication adjustments) are properly tracked. In the US, home use blood test meters must be approved by the Federal Food and Drug Administration before they can be sold.

Finally, there are several influences on blood glucose level aside from food intake. Infection, for instance, tends to change blood glucose levels, as does stress either physical or psychological. Exercise, especially if prolonged or long after the most recent meal, will have an effect as well. In the normal person, maintenance of blood glucose at near constant levels will nevertheless be quite effective.

Causes of abnormal glucose levels			
Persistent hyperglycemia	**Transient hyperglycemia**	**Persistent hypoglycemia**	**Transient hypoglycemia**
Reference range, FBG: 70–110 mg/dl			
Diabetes mellitus	Pheochromocytoma	Insulinoma	Acute alcohol ingestion
Adrenal cortical hyperactivity Cushing's syndrome	Severe liver disease	Adrenal cortical insufficiency Addison's disease	Drugs: salicylates, antituberculosis agents
Hyperthyroidism	Acute stress reaction	Hypopituitarism	Severe liver disease
Acromegaly	Shock	Galactosemia	Several glycogen storage diseases
Obesity	Convulsions	Ectopic insulin production from tumors	Hereditary fructose intolerance

Etymology and use of term

The term 'blood sugar' has colloquial origins. In a physiological context, the term is a misnomer because it refers to glucose, yet other sugars besides glucose are always present. Food contains several different types (e.g., fructose (largely from fruits/table sugar/industrial sweeteners). galactose (milk and dairy products), as well as several food additives such as sorbitol, xylose, maltose, etc.). But because these other sugars are largely inert with regard to the metabolic control system (i.e., that controlled by insulin secretion), since glucose is the dominant controlling signal for metabolic regulation, the term has gained currency, and is used by medical staff and lay folk alike. The table above reflects some of the more technical and closely defined terms used in the medical field.

Blood glucose in birds and reptiles

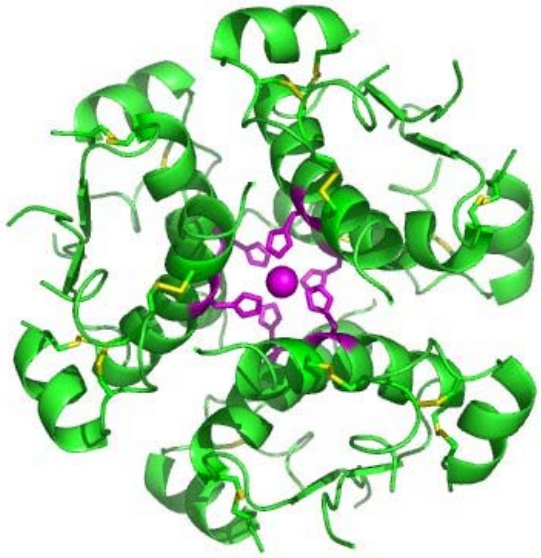
Birds and reptiles process sugars differently. The pancreas is slightly more well developed in birds than in mammals, perhaps as a partial compensation for the lack of saliva and chewing. It produces carbohydrate, fat and protein digesting enzymes which

are secreted into the small intestine. The liver has two distinct lobes each with its own duct leading into the small intestine. The liver, as in mammals, houses the bile, which in birds however is acidic and not alkaline as it is in mammals. Many birds do not have a gall bladder to hold the bile, and it is secreted directly into the pancreatic ducts.

Chapter 3

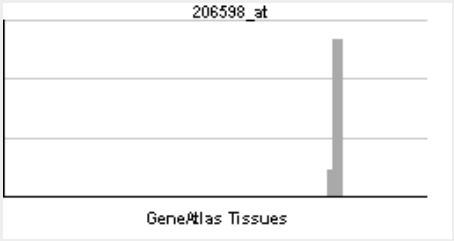
Insulin

Insulin



Computer-generated image of six insulin molecules assembled in a hexamer, highlighting the threefold symmetry, the zinc ions holding it together, and the histidine residues involved in zinc binding. Insulin is stored in the body as a hexamer, while the active form is the monomer.

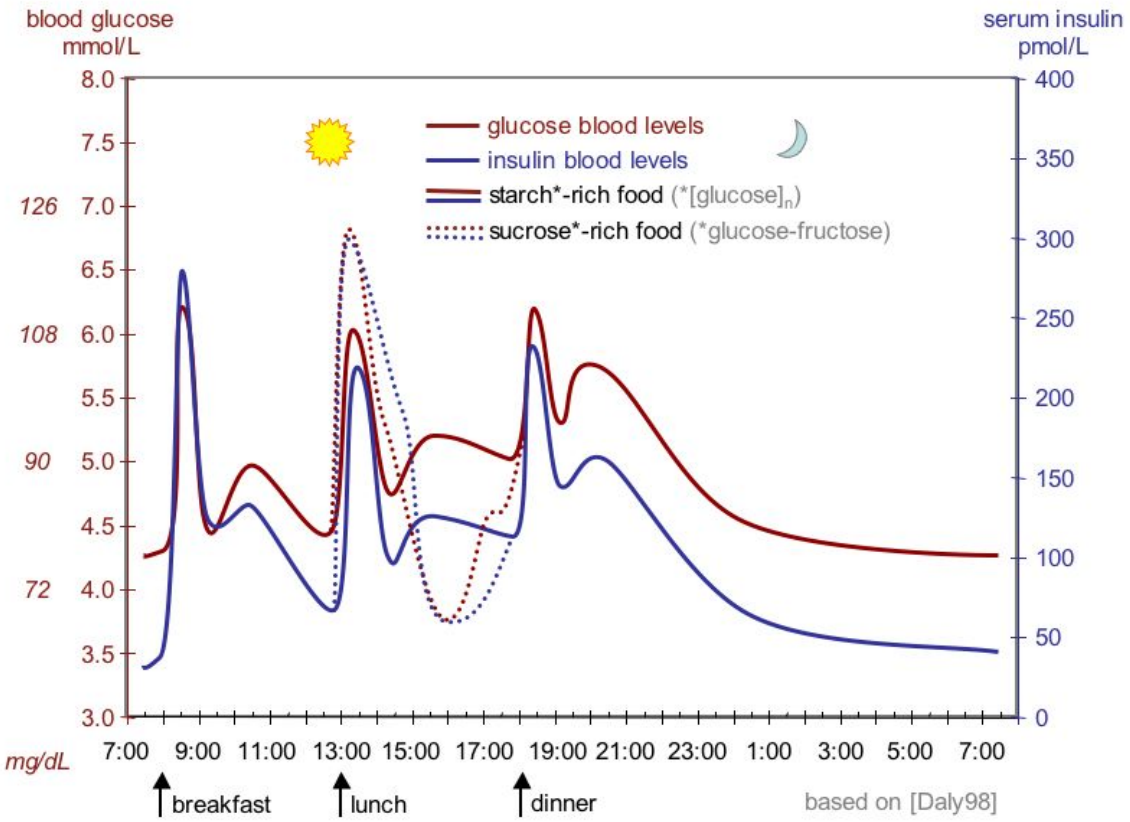
Identifiers	
Symbols	INS;
External IDs	OMIM: 176730 MGI: 96573 HomoloGene: 173 GeneCards: INS Gene
RNA expression pattern	



More reference expression data

Orthologs

Species	Human	Mouse
Entrez	3630	16334
Ensembl	ENSG00000129965	ENSMUSG00000000215
UniProt	P01308	Q5EEX1
RefSeq (mRNA)	NM_000207	NM_008387
RefSeq (protein)	NP_000198	NP_032413
Location (UCSC)	Chr 11: 2.14 - 2.14 Mb	Chr 7: 142.49 - 142.49 Mb
PubMed search		



The idealized diagram shows the fluctuation of blood sugar (red) and the sugar-lowering hormone **insulin** (blue) in humans during the course of a day containing three meals. In addition, the effect of a sugar-rich versus a starch-rich meal is highlighted.

Insulin is a hormone that is central to regulating carbohydrate and fat metabolism in the body. Insulin causes cells in the liver, muscle, and fat tissue to take up glucose from the blood, storing it as glycogen in the liver and muscle.

Insulin stops the use of fat as an energy source by inhibiting the release of glucagon. When insulin is absent, glucose is not taken up by body cells and the body begins to use fat as an energy source or gluconeogenesis; for example, by transfer of lipids from adipose tissue to the liver for mobilization as an energy source. As its level is a central metabolic control mechanism, its status is also used as a control signal to other body systems (such as amino acid uptake by body cells). In addition, it has several other anabolic effects throughout the body.

When control of insulin levels fails, diabetes mellitus will result. As a consequence, insulin is used medically to treat some forms of diabetes mellitus. Patients with Type 1 diabetes mellitus depend on external insulin (most commonly injected subcutaneously) for their survival because the hormone is no longer produced internally. Patients with Type 2 diabetes mellitus are often insulin resistant, and because of such resistance, may suffer from a *relative* insulin deficiency. Some patients with Type 2 diabetes may

eventually require insulin if other medications fail to control blood glucose levels adequately, though this is somewhat uncommon.

Insulin also influences other body functions, such as vascular compliance and cognition. Once insulin enters the human brain, it enhances learning and memory and in particular benefits verbal memory. Enhancing brain insulin signaling by means of intranasal insulin administration also enhances the acute thermoregulatory and glucoregulatory response to food intake, suggesting that central nervous insulin contributes to the control of whole-body energy homeostasis in humans.

Insulin is a peptide hormone composed of 51 amino acids and has a molecular weight of 5808 Da. It is produced in the islets of Langerhans in the pancreas. The name comes from the Latin *insula* for "island". Insulin's structure varies slightly between species of animal. Insulin from animal sources differs somewhat in "strength" (in carbohydrate metabolism control effects) in humans because of those variations. Porcine insulin is especially close to the human version.

Gene

The proinsulin precursor of insulin is encoded by the *INS* gene.

Alleles

A variety of mutant alleles with changes in the coding region have been identified. There is a read-through gene, INS-IGF2, which overlaps with this gene at the 5' region and with the IGF2 gene at the 3' region.

Regulation

There are several regulatory sequences in the promoter region of the human insulin gene, to which transcription factors bind.

In general, the A-boxes bind to Pdx1 factors, E-boxes bind to NeuroD, C-boxes bind to MafA and cAMP response elements to CREB.

There are also silencers that inhibit transcription.

Regulatory sequences and their transcription factors for the insulin gene.

Regulatory sequence	binding transcription factors
ILPR	Par1
A5	Pdx1
negative regulatory element (NRE)	glucocorticoid receptor, Oct1

Z (overlapping NRE and C2)	ISF
C2	Pax4, MafA(?)
E2	USF1/USF2
A3	Pdx1
CREB RE	-
CREB RE	CREB, CREM
A2	-
CAAT enhancer binding (CEB) (partly overlapping A2 and C1)	-
C1	-
E1	E2A, NeuroD1, HEB
A1	Pdx1
G1	-

Protein structure

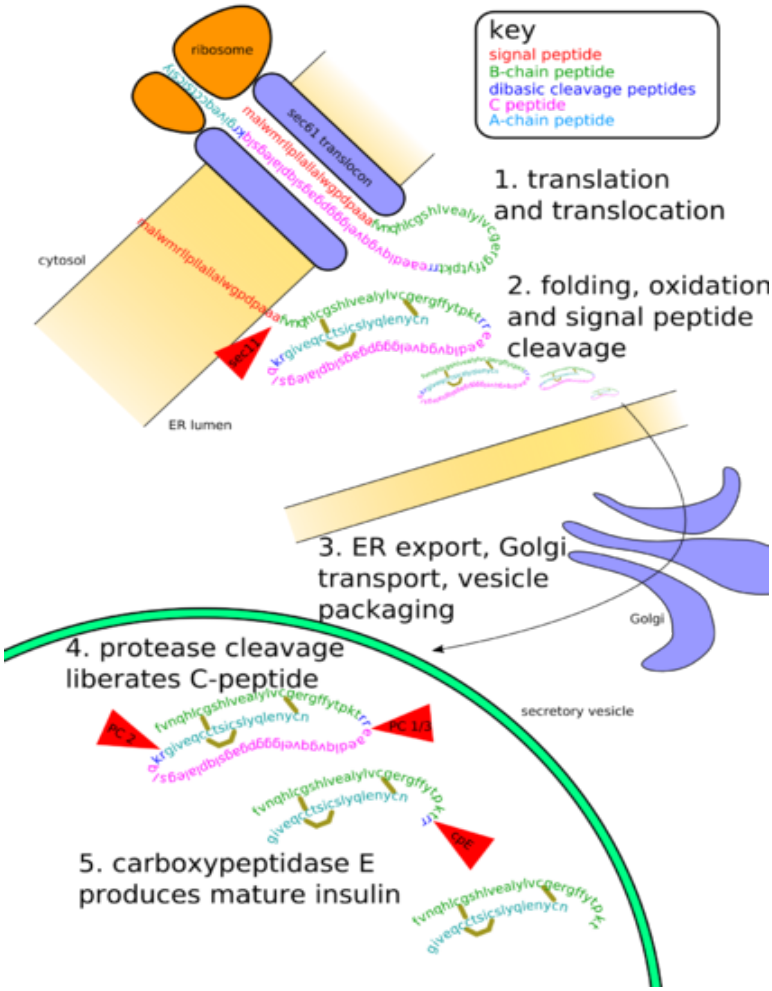
Within vertebrates, the amino acid sequence of insulin is extremely well preserved. Bovine insulin differs from human in only three amino acid residues, and porcine insulin in one. Even insulin from some species of fish is similar enough to human to be clinically effective in humans. Insulin in some invertebrates is quite similar in sequence to human insulin, and has similar physiological effects. The strong homology seen in the insulin sequence of diverse species suggests that it has been conserved across much of animal evolutionary history. The C-peptide of proinsulin (discussed later), however, differs much more amongst species; it is also a hormone, but a secondary one.

Insulin is produced and stored in the body as a hexamer (a unit of six insulin molecules), while the active form is the monomer. The hexamer is an inactive form with long-term stability, which serves as a way to keep the highly reactive insulin protected, yet readily available. The hexamer-monomer conversion is one of the central aspects of insulin formulations for injection. The hexamer is far more stable than the monomer, which is desirable for practical reasons, however the monomer is a much faster reacting drug because diffusion rate is inversely related to particle size. A fast reacting drug means that insulin injections do not have to precede mealtimes by hours, which in turn gives diabetics more flexibility in their daily schedule. Insulin can aggregate and form fibrillar interdigitated beta-sheets. This can cause injection amyloidosis, and prevents the storage of insulin for long periods.

Synthesis, physiological effects, and degradation

Synthesis

Insulin is produced in the pancreas and released when any of the several stimuli are detected. The stimuli include ingested protein and glucose in the blood produced from digested food. Carbohydrate can be polymers of simple sugars or the simple sugars themselves. If the carbohydrate includes glucose then that glucose will be absorbed into the bloodstream and blood glucose level will begin to rise. In target cells, insulin initiates a signal transduction, which has the effect of increasing glucose uptake and storage. Finally, insulin is degraded, terminating the response.



Insulin undergoes extensive posttranslational modification along the production pathway. Production and secretion are largely independent; prepared insulin is stored awaiting secretion. Both C-peptide and mature insulin are biologically active. Cell components and proteins in this image are not to scale.

In mammals, insulin is synthesized in the pancreas within the beta cells (β-cells) of the islets of Langerhans. One million to three million islets of Langerhans (pancreatic islets) form the endocrine part of the pancreas, which is primarily an exocrine gland. The endocrine portion accounts for only 2% of the total mass of the pancreas. Within the islets of Langerhans, beta cells constitute 60–80% of all the cells.

In beta cells, insulin is synthesized from the proinsulin precursor molecule by the action of proteolytic enzymes, known as prohormone convertases (PC1 and PC2), as well as the exoprotease carboxypeptidase E. These modifications of proinsulin remove the center portion of the molecule (i.e., C-peptide), from the C- and N- terminal ends of proinsulin. The remaining polypeptides (51 amino acids in total), the B- and A- chains, are bound together by disulfide bonds/disulphide bonds. Confusingly, the primary sequence of proinsulin goes in the order "B-C-A", since B and A chains were identified on the basis of mass, and the C-peptide was discovered after the others.

The endogenous production of insulin is regulated in several steps along the synthesis pathway:

- At transcription from the insulin gene
- In mRNA stability
- At the mRNA translation
- In the posttranslational modifications

It has been shown that insulin and its related proteins, are also produced inside the brain and that reduced levels of these proteins are linked to Alzheimer's disease.

Release

Beta cells in the islets of Langerhans release insulin in two phases. The first phase insulin release is rapidly triggered in response to increased blood glucose levels. The second phase is a sustained, slow release of newly formed vesicles that are triggered independently of sugar. The description of first phase release is as follows:

- Glucose enters the beta cells through the glucose transporter GLUT2
- Glucose goes into glycolysis and the respiratory cycle where multiple high-energy ATP molecules are produced by oxidation
- Dependent on the ATP:ADP ratio, and hence blood glucose levels, the ATP-dependent potassium channels (K^+) close and the cell membrane depolarizes
- On depolarization, voltage controlled calcium channels (Ca^{2+}) open and calcium flows into the cells
- An increased calcium level causes activation of phospholipase C, which cleaves the membrane phospholipid phosphatidyl inositol 4,5-bisphosphate into inositol 1,4,5-triphosphate and diacylglycerol .
- Inositol 1,4,5-triphosphate (IP3) binds to receptor proteins in the membrane of endoplasmic reticulum (ER). This allows the release of Ca^{2+} from the ER via IP3 gated channels, and further raises the cell concentration of calcium.

- Significantly increased amounts of calcium in the cells causes release of previously synthesized insulin, which has been stored in secretory vesicles

This is the main mechanism for release of insulin. In addition some insulin release takes place generally with food intake, not just glucose or carbohydrate intake, and the beta cells are also somewhat influenced by the autonomic nervous system. The signaling mechanisms controlling these linkages are not fully understood.

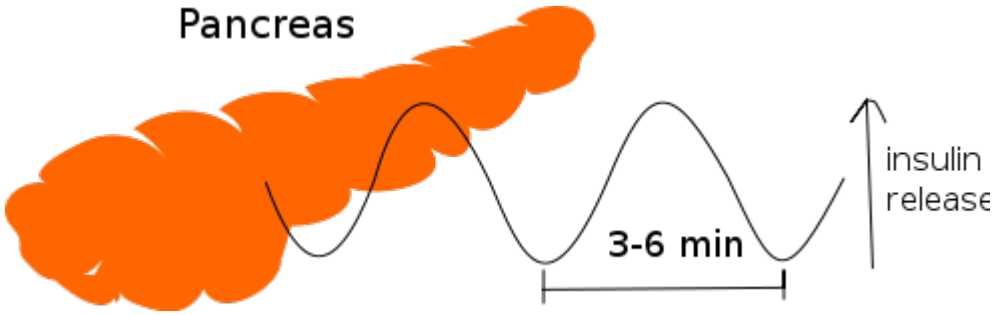
Other substances known to stimulate insulin release include amino acids from ingested proteins, acetylcholine released from vagus nerve endings (parasympathetic nervous system), gastrointestinal hormones released by enteroendocrine cells of intestinal mucosa and glucose-dependent insulinotropic peptide (GIP). Three amino acids (alanine, glycine and arginine) act similarly to glucose by altering the beta cell's membrane potential. Acetylcholine triggers insulin release through phospholipase C, while the last acts through the mechanism of adenylate cyclase.

The sympathetic nervous system (via α_2-adrenergic stimulation as demonstrated by the agonists clonidine or methyldopa) inhibit the release of insulin. However, it is worth noting that circulating adrenaline will activate β_2-Receptors on the Beta cells in the pancreatic Islets to promote insulin release. This is important since muscle cannot benefit from the raised blood sugar resulting from adrenergic stimulation (increased gluconeogenesis and glycogenolysis from the low blood insulin: glucagon state) unless insulin is present to allow for GLUT-4 translocation in the tissue. Therefore, beginning with direct innervation, norepinephrine inhibits insulin release via α_2-receptors, then subsequently, circulating adrenaline from the adrenal medulla will stimulate β_2-receptors thereby promoting insulin release.

When the glucose level comes down to the usual physiologic value, insulin release from the beta cells slows or stops. If blood glucose levels drop lower than this, especially to dangerously low levels, release of hyperglycemic hormones (most prominently glucagon from Islet of Langerhans' alpha cells) forces release of glucose into the blood from cellular stores, primarily liver cell stores of glycogen. By increasing blood glucose, the hyperglycemic hormones prevent or correct life-threatening hypoglycemia. Release of insulin is strongly inhibited by the stress hormone norepinephrine (noradrenaline), which leads to increased blood glucose levels during stress.

Evidence of impaired first phase insulin release can be seen in the glucose tolerance test, demonstrated by a substantially elevated blood glucose level at 30 minutes, a marked drop by 60 minutes, and a steady climb back to baseline levels over the following hourly time points.

Oscillations



Insulin release from pancreas oscillates with a period of 3–6 minutes

Even during digestion, generally one or two hours following a meal, insulin release from pancreas is not continuous, but oscillates with a period of 3–6 minutes, changing from generating a blood insulin concentration more than ~800 pmol/l to less than 100 pmol/l. This is thought to avoid downregulation of insulin receptors in target cells and to assist the liver in extracting insulin from the blood. This oscillation is important to consider when administering insulin-stimulating medication, since it is the oscillating blood concentration of insulin release, which should, ideally, be achieved, not a constant high concentration. This may be achieved by delivering insulin rhythmically to the portal vein or by islet cell transplantation to the liver. Future insulin pumps hope to address this characteristic.

Signal transduction

There are special transporter proteins in cell membranes through which glucose from the blood can enter a cell. These transporters are, indirectly, under blood insulin's control in certain body cell types (e.g., muscle cells). Low levels of circulating insulin, or its absence, will prevent glucose from entering those cells (e.g., in Type 1 diabetes). However, more commonly there is a decrease in the sensitivity of cells to insulin (e.g., the reduced insulin sensitivity characteristic of Type 2 diabetes), resulting in decreased glucose absorption. In either case, there is 'cell starvation', weight loss, sometimes extreme. In a few cases, there is a defect in the release of insulin from the pancreas. Either way, the effect is, characteristically, the same: elevated blood glucose levels.

Activation of insulin receptors leads to internal cellular mechanisms that directly affect glucose uptake by regulating the number and operation of protein molecules in the cell membrane that transport glucose into the cell. The genes that specify the proteins that make up the insulin receptor in cell membranes have been identified and the structures of the interior, transmembrane section, and the extra-membrane section of receptor have been solved.

Two types of tissues are most strongly influenced by insulin, as far as the stimulation of glucose uptake is concerned: muscle cells (myocytes) and fat cells (adipocytes). The former are important because of their central role in movement, breathing, circulation,

etc., and the latter because they accumulate excess food energy against future needs. Together, they account for about two-thirds of all cells in a typical human body.

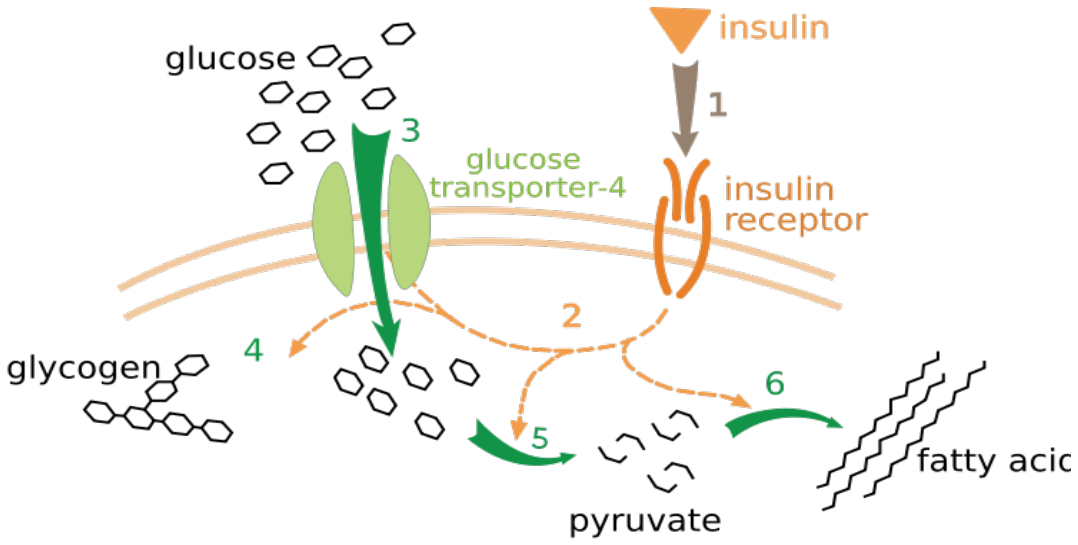
Insulin binds to the extracellular portion of the alpha subunits of the insulin receptor. This in turn causes an conformational change in the insulin receptor that activates the kinase domain that resides on the intracellular portion of the beta subunits. The activated kinase domain autophosphorylates tyrosine residues on the C-terminus of the receptor as well as tyrosine residues in the IRS-1 protein.

1. phosphorylated IRS-1 in turn binds to and activates phosphoinositol 3 kinase (PI3K)
2. PI3K catalyzes the reaction PIP2 + ATP → PIP3
3. PIP3 activates protein kinase B (PKB)
4. PKB phosphorylates glycogen synthase kinase (GSK) and thereby inactivates GSK
5. GSK can no longer phosphorylate glycogen synthase (GS)
6. unphospohrylated GS makes more glycogen
7. PKB also facilitates vesicle fusion resulting in an increase in GLUT4 transporters in the plasma membrane

Low-frequency internal motion

According to the study of Raman spectra, a low-frequency wave number of 22 cm^{-1} has been observed for insulin molecules. Subsequently, it was identified as the accordion-like vibration of the helix (B9-B19) in the B-chain of insulin.

Physiological effects



Effect of insulin on glucose uptake and metabolism. Insulin binds to its receptor (1), which in turn starts many protein activation cascades (2). These include: translocation of

Glut-4 transporter to the plasma membrane and influx of glucose (3), glycogen synthesis (4), glycolysis (5) and fatty acid synthesis (6).

The actions of insulin on the global human metabolism level include:

- Control of cellular intake of certain substances, most prominently glucose in muscle and adipose tissue (about ⅔ of body cells).
- Increase of DNA replication and protein synthesis via control of amino acid uptake.
- Modification of the activity of numerous enzymes.

The actions of insulin on cells include:

- Increased glycogen synthesis – insulin forces storage of glucose in liver (and muscle) cells in the form of glycogen; lowered levels of insulin cause liver cells to convert glycogen to glucose and excrete it into the blood. This is the clinical action of insulin, which is directly useful in reducing high blood glucose levels as in diabetes.
- Increased fatty acid synthesis – insulin forces fat cells to take in blood lipids, which are converted to triglycerides; lack of insulin causes the reverse.
- Increased esterification of fatty acids – forces adipose tissue to make fats (i.e., triglycerides) from fatty acid esters; lack of insulin causes the reverse.
- Decreased proteolysis – decreasing the breakdown of protein.
- Decreased lipolysis – forces reduction in conversion of fat cell lipid stores into blood fatty acids; lack of insulin causes the reverse.
- Decreased gluconeogenesis – decreases production of glucose from non-sugar substrates, primarily in the liver (remember, the vast majority of endogenous insulin arriving at the liver never leaves the liver); lack of insulin causes glucose production from assorted substrates in the liver and elsewhere.
- Decreased autophagy - decreased level of degradation of damaged organelles. Postprandial levels inhibit autophagy completely.
- Increased amino acid uptake – forces cells to absorb circulating amino acids; lack of insulin inhibits absorption.
- Increased potassium uptake – forces cells to absorb serum potassium; lack of insulin inhibits absorption. Insulin's increase in cellular potassium uptake lowers potassium levels in blood.
- Arterial muscle tone – forces arterial wall muscle to relax, increasing blood flow, especially in micro arteries; lack of insulin reduces flow by allowing these muscles to contract.
- Increase in the secretion of hydrochloric acid by Parietal cells in the stomach.

Degradation

Once an insulin molecule has docked onto the receptor and effected its action, it may be released back into the extracellular environment, or it may be degraded by the cell. The two primary sites for insulin clearance are the liver and kidney. The liver clears most

insulin during first-pass transit, while the kidney clears most of the insulin in systemic circulation. Degradation normally involves endocytosis of the insulin-receptor complex followed by the action of insulin degrading enzyme. It has been estimated that an insulin molecule produced endogenously by the pancreatic beta cells is degraded within approximately one hour after its initial release into circulation (insulin half-life ~ 4–6 minutes).

Hypoglycemia

Although other cells can use other fuels for a while (most prominently fatty acids), neurons depend on glucose as a source of energy in the non-starving human. They do not require insulin to absorb glucose, unlike muscle and adipose tissue, and they have very small internal stores of glycogen. Glycogen stored in liver cells (unlike glycogen stored in muscle cells) can be converted to glucose, and released into the blood, when glucose from digestion is low or absent, and the glycerol backbone in triglycerides can also be used to produce blood glucose.

Sufficient lack of glucose and scarcity of these sources of glucose can dramatically make itself manifest in the impaired functioning of the central nervous system; dizziness, speech problems, and even loss of consciousness, can occur. Low glucose is known as hypoglycemia or, in cases producing unconsciousness, "hypoglycemic coma" (sometimes termed "insulin shock" from the most common causative agent). Endogenous causes of insulin excess (such as an insulinoma) are very rare, and the overwhelming majority of insulin-excess induced hypoglycemia cases are iatrogenic and usually accidental. There have been a few reported cases of murder, attempted murder, or suicide using insulin overdoses, but most insulin shocks appear to be due to errors in dosage of insulin (e.g., 20 units of insulin instead of 2) or other unanticipated factors (didn't eat as much as anticipated, or exercised more than expected, or unpredicted kinetics of the subcutaneously injected insulin itself).

Possible causes of hypoglycemia include:

- External insulin (usually injected subcutaneously).
- Oral hypoglycemic agents (e.g., any of the sulfonylureas, or similar drugs, which increase insulin release from beta cells in response to a particular blood glucose level).
- Ingestion of low-carbohydrate sugar substitutes in people without diabetes or with type 2 diabetes. Animal studies show these can trigger insulin release, albeit in much smaller quantities than sugar, according to a report in *Discover* magazine, August 2004, p 18. (This can never be a cause of hypoglycemia in patients with type 1 diabetes since there is no endogenous insulin production to stimulate.)

Diseases and syndromes

There are several conditions in which insulin disturbance is pathologic:

- Diabetes mellitus – general term referring to all states characterized by hyperglycemia.
    - Type 1 – autoimmune-mediated destruction of insulin producing beta cells in the pancreas resulting in absolute insulin deficiency.
    - Type 2 – multifactoral syndrome with combined influence of genetic susceptibility and influence of environmental factors, the best known being obesity, age, and physical inactivity, resulting in insulin resistance in cells requiring insulin for glucose absorption. This form of diabetes is strongly inherited.
    - Other types of impaired glucose tolerance.
- Insulinoma - a tumor of pancreatic beta cells producing excess of insulin or reactive hypoglycemia.
- Metabolic syndrome – a poorly understood condition first called Syndrome X by Gerald Reaven, Reaven's Syndrome after Reaven, CHAOS in Australia (from the signs that seem to travel together). It is currently not clear whether these signs have a single, treatable cause, or are the result of body changes leading to type 2 diabetes. It is characterized by elevated blood pressure, dyslipidemia (disturbances in blood cholesterol forms and other blood lipids), and increased waist circumference (at least in populations in much of the developed world). The basic underlying cause may be the insulin resistance of type 2 diabetes, which is a diminished capacity for insulin response in some tissues (e.g., muscle, fat) to respond to insulin. Commonly, morbidities such as essential hypertension, obesity, Type 2 diabetes, and cardiovascular disease (CVD) develop.
- Polycystic ovary syndrome – a complex syndrome in women in the reproductive years where there is anovulation and androgen excess commonly displayed as hirsutism. In many cases of PCOS insulin resistance is present.

As a medication

Insulin vial

Biosynthetic "human" insulin is now manufactured for widespread clinical use using recombinant DNA technology. More recently, researchers have succeeded in introducing the gene for human insulin into plants and in producing insulin in plants, specifically safflower. It is anticipated that this technique will reduce production costs.

Several of these are slightly modified versions of human insulin that, while having a clinical effect on blood glucose levels as though they were exact copies, have been designed to have somewhat different absorption or duration of action characteristics. They are usually referred to as "insulin analogues". For instance, the first available, insulin lispro, does not exhibit a delayed absorption effect found in "regular" insulin, and begins to have effect in as little as 15 minutes. Other rapid acting analogues are NovoRapid and Apidra with similar profiles. All are rapidly absorbed due to a mutation in the sequence that prevents the insulin analogue in forming dimers and hexamers. Instead, the insulin molecule is a monomer, which is more rapidly absorbed. Using it, therefore, does not require the pre-planning required for other insulins that begin to take effect much later (up to many hours) after administration. Another type is extended release insulin; the first of these was Lantus (insulin glargine). These have a steady effect for the entire time they are active, without the peak and drop of effect in other insulins; typically, they continue to have an insulin effect for an extended period from 18 to 24 hours. Similar another protracted insulin analogue "Levemir" is based on a fatty acid acylation approach. A fatty acid (myristyric acid) is attached to this analogue, which in turn associates the insulin molecule to the abundant serum albumin. This in turn extends the effect and in addition it reduces the risk of hypoglycemia. Both protracted analogues need to be taken only once-daily and are very much used in the type 1 diabetes market as

the basal insulin. A mix combination of a rapid acting and a protracted insulin is also available for the patients making it more likely for the patient to achieve an insulin profile that mimics that of the body´s own insulin release.

Unlike many medicines, insulin currently cannot be taken orally. Like nearly all other proteins introduced into the gastrointestinal tract, it is reduced to fragments (even single amino acid components), whereupon all "insulin activity" is lost. There has been some research into ways to protect insulin from the digestive tract, so that it can be administered orally or sublingually. While experimental, several companies now have various formulations in human clinical trials.

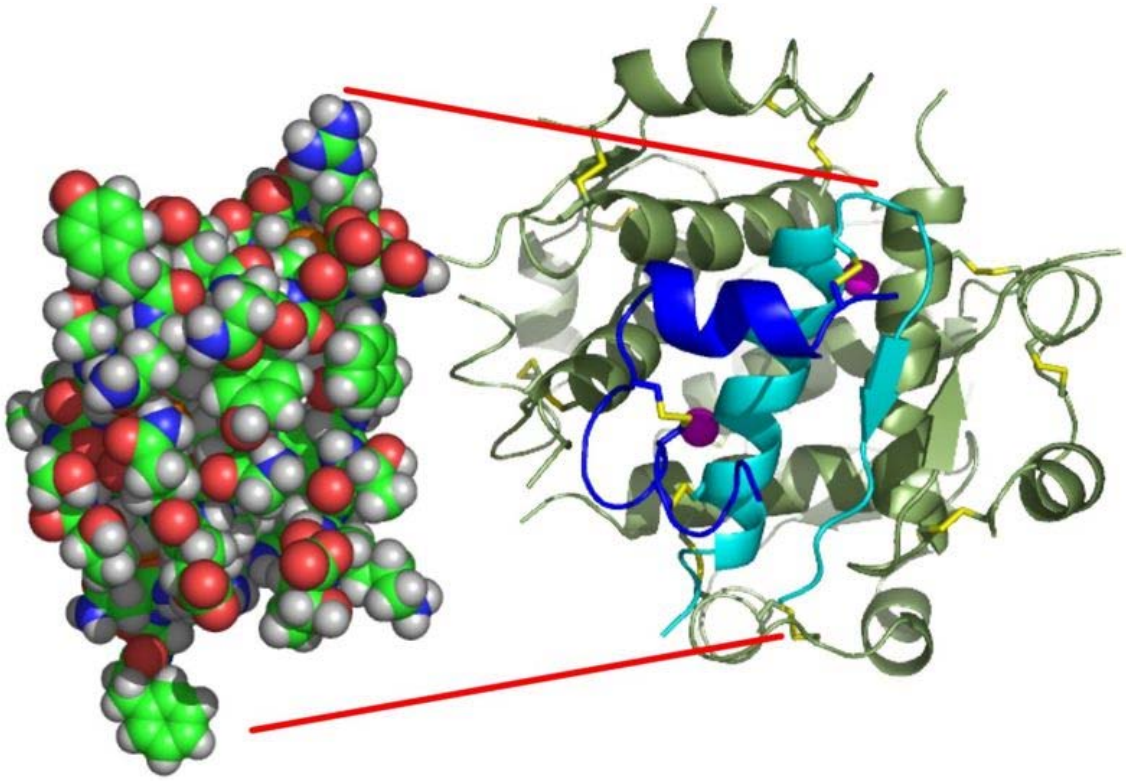
Insulin is usually taken as subcutaneous injections by single-use syringes with needles, an insulin pump, or by repeated-use insulin pens with needles.

History

Discovery and characterization

In 1869 Paul Langerhans, a medical student in Berlin, was studying the structure of the pancreas under a microscope when he identified some previously un-noticed tissue clumps scattered throughout the bulk of the pancreas. The function of the "little heaps of cells," later known as the *Islets of Langerhans*, was unknown, but Edouard Laguesse later suggested that they might produce secretions that play a regulatory role in digestion. Paul Langerhans' son, Archibald, also helped to understand this regulatory role. The term *insulin* origins from *insula*, the Latin word for islet/island.

In 1889, the Polish-German physician Oscar Minkowski in collaboration with Joseph von Mering removed the pancreas from a healthy dog to test its assumed role in digestion. Several days after the dog's pancreas was removed, Minkowski's animal keeper noticed a swarm of flies feeding on the dog's urine. On testing the urine they found that there was sugar in the dog's urine, establishing for the first time a relationship between the pancreas and diabetes. In 1901, another major step was taken by Eugene Opie, when he clearly established the link between the Islets of Langerhans and diabetes: *Diabetes mellitus ... is caused by destruction of the islets of Langerhans and occurs only when these bodies are in part or wholly destroyed.* Before his work, the link between the pancreas and diabetes was clear, but not the specific role of the islets.



The structure of insulin. The left side is a space-filling model of the insulin monomer, believed to be biologically active. Carbon is green, hydrogen white, oxygen red, and nitrogen blue. On the right side is a ribbon diagram of the insulin hexamer, believed to be the stored form. A monomer unit is highlighted with the A chain in blue and the B chain in cyan. Yellow denotes disulfide bonds, and magenta spheres are zinc ions.

Over the next two decades, several attempts were made to isolate whatever it was the islets produced as a potential treatment. In 1906 George Ludwig Zuelzer was partially successful treating dogs with pancreatic extract but was unable to continue his work. Between 1911 and 1912, E.L. Scott at the University of Chicago used aqueous pancreatic extracts and noted *a slight diminution of glycosuria* but was unable to convince his director of his work's value; it was shut down. Israel Kleiner demonstrated similar effects at Rockefeller University in 1915, but his work was interrupted by World War I and he did not return to it.

Nicolae Paulescu, a professor of physiology at the University of Medicine and Pharmacy in Bucharest, was the first one to isolate insulin, which he called at that time pancrein, and published in 1921 the work that he had carried out in Bucharest. Use of his techniques was patented in Romania, though no clinical use resulted.

In October 1920 Canadian Frederick Banting was reading one of Minkowski's papers and concluded that it is the very digestive secretions that Minkowski had originally studied

that were breaking down the islet secretion(s), thereby making it impossible to extract successfully. He jotted a note to himself: *Ligate pancreatic ducts of the dog. Keep dogs alive till acini degenerate leaving islets. Try to isolate internal secretion of these and relieve glycosurea.*

The idea was that the pancreas's internal secretion, which supposedly regulates sugar in the bloodstream, might hold the key to the treatment of diabetes. A surgeon by training, Banting knew that certain arteries could be tied off that would lead to atrophy of most of the pancreas while leaving the islets of Langerhans intact. He theorized that a relatively pure extract could be made from the islets once most of the rest of pancreas was gone.

In the Spring of 1921 Banting traveled to Toronto to explain his idea to J.J.R. Macleod who was Professor of Physiology at the University of Toronto, and asked Macleod if he could use his lab space to test the idea. Macleod was initially skeptical, but eventually agreed to let Banting use his lab space while he was on vacation for the summer. He also supplied Banting with ten dogs to experiment on, and two medical students, Charles Best and Clark Noble, to use as lab assistants, before leaving for Scotland. Since Banting required only one lab assistant, Best and Noble flipped a coin to see which would assist Banting for the first half of the summer. Best won the coin toss, and took the first shift as Banting's assistant. Loss of the coin toss may have proved unfortunate for Noble, given that Banting decided to keep Best for the entire summer, and eventually shared half his Nobel Prize money and a large part of the credit for the discovery of insulin with the winner of the toss. Had Noble won the toss, his career might have taken a different path. Banting's method was to tie a ligature (string) around the pancreatic duct, and, when examined several weeks later, the pancreatic digestive cells had died and been absorbed by the immune system, leaving thousands of islets. They then isolated an extract from these islets, producing what they called *isletin* (what we now know as insulin), and tested this extract on the dogs. Banting and Best were then able to keep a pancreatectomized dog named Alpha alive for the rest of the summer by injecting her with the crude extract they had prepared. Removal of the pancreas in test animals essentially mimics diabetes, leading to elevated blood glucose levels. Alpha was able to remain alive because the extracts, containing isletin, were able to lower her blood glucose levels.

Banting and Best presented their results to Macleod on his return to Toronto in the fall of 1921, but Macleod pointed out flaws with the experimental design, and suggested the experiments be repeated with more dogs and better equipment. He then supplied Banting and Best with a better laboratory, and began paying Banting a salary from his research grants. Several weeks later, it was clear the second round of experiments was also a success; and Macleod helped publish their results privately in Toronto that November. However, they needed six weeks to extract the isletin, which forced considerable delays. Banting suggested that they try to use fetal calf pancreas, which had not yet developed digestive glands; he was relieved to find that this method worked well. With the supply problem solved, the next major effort was to purify the extract. In December 1921, Macleod invited the biochemist James Collip to help with this task, and, within a month, the team felt ready for a clinical test.

On January 11, 1922, Leonard Thompson, a 14-year-old diabetic who lay dying at the Toronto General Hospital, was given the first injection of insulin. However, the extract was so impure that Thompson suffered a severe allergic reaction, and further injections were canceled. Over the next 12 days, Collip worked day and night to improve the ox-pancreas extract, and a second dose was injected on January 23. This was completely successful, not only in having no obvious side-effects but also in completely eliminating the glycosuria sign of diabetes. The first American patient was Elizabeth Hughes Gossett, the daughter of the governor of New York. The first patient treated in the U.S. was future woodcut artist James D. Havens; Dr. John Ralston Williams imported insulin from Toronto to Rochester, New York, to treat Havens.

Children dying from diabetic keto-acidosis were kept in large wards, often with 50 or more patients in a ward, mostly comatose. Grieving family members were often in attendance, awaiting the (until then, inevitable) death.

In one of medicine's more dramatic moments Banting, Best, and Collip went from bed to bed, injecting an entire ward with the new purified extract. Before they had reached the last dying child, the first few were awakening from their coma, to the joyous exclamations of their families.

Banting and Best never worked well with Collip, regarding him as something of an interloper, and Collip left the project soon after.

Over the spring of 1922, Best managed to improve his techniques to the point where large quantities of insulin could be extracted on demand, but the preparation remained impure. The drug firm Eli Lilly and Company had offered assistance not long after the first publications in 1921, and they took Lilly up on the offer in April. In November, Lilly made a major breakthrough and were able to produce large quantities of highly refined insulin. Insulin was offered for sale shortly thereafter.

Purified animal-sourced insulin was the only type of insulin available to diabetics until genetic breakthroughs occurred later with medical research. The amino-acid structure of insulin was characterized in the 1950s and the first synthetic insulin was produced simultaneously in the labs of Panayotis Katsoyannis at the University of Pittsburgh and Helmut Zahn at RWTH Aachen University in the early 1960s.

The first genetically-engineered, synthetic "human" insulin was produced in a laboratory in 1977 by Herbert Boyer using E. coli. Partnering with Genentech founded by Boyer, Eli Lilly and Company went on in 1982 to sell the first commercially available biosynthetic human insulin under the brand name Humulin. The vast majority of insulin currently used worldwide is now biosynthetic recombinant "human" insulin or its analogs.

Chapter 4

Diabetes Mellitus Type 1

Diabetes mellitus type 1

Universal blue circle symbol for diabetes.

ICD-10	E10
ICD-9	250.01
OMIM	222100
DiseasesDB	3649
MedlinePlus	000305
eMedicine	med/546
MeSH	D003922

Diabetes mellitus type 1 (Type 1 diabetes, IDDM, or, obsoletely, juvenile diabetes) is a form of diabetes mellitus that results from autoimmune destruction of insulin-producing beta cells of the pancreas. The subsequent lack of insulin leads to increased blood and urine glucose. The classical symptoms of polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased hunger), and weight loss result.

Type 1 diabetes is fatal unless treated with insulin. Injection is the most common method of administering insulin; insulin pumps and inhaled insulin have been available at various times. Pancreas and islet transplants have been used to treat type 1 diabetes; however, islet transplants are currently still at the experimental trial stage.

Most people who develop type 1 are otherwise healthy. Although the cause of type 1 diabetes is still not fully understood it is believed to be of immunological origin.

Type 1 can be distinguished from type 2 diabetes via a C-peptide assay, which measures endogenous insulin production.

Type 1 treatment must be continued indefinitely in all cases. Treatment need not significantly impair normal activities, if sufficient patient training, awareness, appropriate care, discipline in testing and dosing of insulin is taken. However, treatment is burdensome for many people. Complications may be associated with both low blood sugar and high blood sugar. Low blood sugar may lead to seizures or episodes of unconsciousness and requires emergency treatment. High blood sugar may lead to increased tiredness and can also result in long term damage to organs.

Signs and symptoms

The classical symptoms of type 1 diabetes include: polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased hunger), tiredness, and weight loss.

Causes and risk factors

Evidence so far indicate that the development of diabetes type I is induced by more or less a combination of genetic susceptibility, a diabetogenic trigger and exposure to a driving antigen. Many risk factors have been suggested, and there is an ongoing research into the influence of individual factors, and whether some may be regarded as sufficient to cause the disease by themselves or only in addition to other risk factors.

Genetics

Type 1 diabetes is a polygenic disease, meaning many different genes contribute to its expression. Depending on locus or combination of loci, it can be dominant, recessive, or somewhere in between. The strongest gene, IDDM1, is located in the MHC Class II region on chromosome 6, at staining region 6p21. Certain variants of this gene increases the risk for decreased histocompatibility characteristic of type 1. Such variants include DRB1 0401, DRB1 0402, DRB1 0405, DQA 0301, DQB1 0302 and DQB1 0201, which are common in North Americans of European ancestry and in Europeans. There are also variants that appear to be protective.

Environmental factors

Environmental factors can strongly influence expression of type 1. A study showed that for identical twins, when one twin had type 1 diabetes, the other twin only had type 1 30%–50% of the time. Despite having exactly the same genome, one twin had the disease, where the other did not; this suggests that environmental factors, in addition to genetic factors, can influence disease prevalence. Other indications of environmental influence include the presence of a 10-fold difference in difference among Caucasians living in different areas of Europe, and a tendency to acquire the incidence of the disease of the destination country for people who migrate.

Virus

One theory, discussed by DeLisa Fairweather & Noel R. Rose, among others, proposes that type 1 diabetes is a virally triggered autoimmune response in which the immune system attacks virus infected cells along with the beta cells in the pancreas. The Coxsackie virus family or Rubella is implicated, although the evidence is inconclusive. In type 1, pancreatic beta cells in the Islets of Langerhans are destroyed decreasing endogenous insulin production. This distinguishes type 1's origin from type 2 DM. The type of diabetes a patient has is determined only by the cause—fundamentally by whether the patient is insulin resistant (type 2) or insulin deficient without insulin resistance (type 1).

This vulnerability is not shared by everyone, for not everyone infected by the suspected organisms develops type 1 diabetes. This has suggested presence of a genetic vulnerability and there is indeed an observed inherited tendency to develop type 1. It has been traced to particular HLA genotypes, though the connection between them and the triggering of an auto-immune reaction is still poorly understood.

Diet

There is a growing body of evidence that diet may play a role in the development of type 1 diabetes, through influencing gut flora, intestinal permeability, and immune function in the gut; wheat in particular has been shown to have a connection to the development of type 1 diabetes, although the relationship is poorly understood.

Some researchers believe that the autoimmune response is influenced by antibodies against cow's milk proteins. No connection has been established between autoantibodies, antibodies to cow's milk proteins, and type 1 diabetes. A subtype of type 1 (identifiable by the presence of antibodies against beta cells) typically develops slowly and so is often confused with type 2. In addition, a small proportion of type 2 cases manifest a genetic form of the disease called maturity onset diabetes of the young (MODY).

Vitamin D in doses of 2000 IU per day given during the first year of a child's life has been connected in one study in Northern Finland (where intrinsic production of Vitamin

D is low due to low natural light levels) with an 80% reduction in the risk of getting type 1 diabetes later in life. The causal connection, if any, is obscure.

Short breast-feeding period and short attendance to day care is associated with the risk of type 1 diabetes in Czech children.

Chemicals and drugs

Some chemicals and drugs preferentially destroy pancreatic cells. Pyrinuron (Vacor, N-3-pyridylmethyl-N'-p-nitrophenyl urea), a rodenticide introduced in the United States in 1976, selectively destroys pancreatic beta cells, resulting in type 1 diabetes after accidental or intentional ingestion. Vacor was withdrawn from the U.S. market in 1979, but is still used in some countries. Zanosar is the trade name for streptozotocin, an antibiotic and antineoplastic agent used in chemotherapy for pancreatic cancer; it also kills beta cells, resulting in loss of insulin production. Other pancreatic problems, including trauma, pancreatitis or tumors (either malignant or benign), can also lead to loss of insulin production.

Pathophysiology

The pathophysiology in diabetes type I is basically a destruction of beta cells in the pancreas, regardless of which risk factors or causative entities have been present.

Individual risk factors can have separate pathophysiological processes to, in turn, cause this beta cell destruction. Still, a process that appears to be common to most risk factors is an autoimmune response towards beta cells, involving an expansion of autoreactive CD4+ and CD8+ T helper cells, autoantibody-producing B cells and activation of the innate immune system.

Diagnosis

2006 WHO Diabetes criteria

Condition	2 hour glucose	Fasting glucose
	mmol/l(mg/dl)	mmol/l(mg/dl)
Normal	<7.8 (<140)	<6.1 (<110)
Impaired fasting glycaemia	<7.8 (<140)	≥ 6.1(≥110) & <7.0(<126)
Impaired glucose tolerance	≥7.8 (≥140)	<7.0 (<126)
Diabetes mellitus	≥11.1 (≥200)	≥7.0 (≥126)

Diabetes mellitus is characterized by recurrent or persistent hyperglycemia, and is diagnosed by demonstrating any one of the following:

- Fasting plasma glucose level at or above 7.0 mmol/L (126 mg/dL).
- Plasma glucose at or above 11.1 mmol/L (200 mg/dL) two hours after a 75 g oral glucose load as in a glucose tolerance test.

- Symptoms of hyperglycemia and casual plasma glucose at or above 11.1 mmol/L (200 mg/dL).
- Glycated hemoglobin (hemoglobin A1C) at or above 6.5. (This criterion was recommended by the American Diabetes Association in 2010; it has yet to be adopted by the WHO.)

About a quarter of people with new type 1 diabetes have developed some degree of diabetic ketoacidosis (a type of metabolic acidosis which is caused by high concentrations of ketone bodies, formed by the breakdown of fatty acids and the deamination of amino acids) by the time the diabetes is recognized. The diagnosis of other types of diabetes is usually made in other ways. These include ordinary health screening, detection of hyperglycemia during other medical investigations, and secondary symptoms such as vision changes or unexplainable fatigue. Diabetes is often detected when a person suffers a problem that is frequently caused by diabetes, such as a heart attack, stroke, neuropathy, poor wound healing or a foot ulcer, certain eye problems, certain fungal infections, or delivering a baby with macrosomia or hypoglycemia.

A positive result, in the absence of unequivocal hyperglycemia, should be confirmed by a repeat of any of the above-listed methods on a different day. Most physicians prefer to measure a fasting glucose level because of the ease of measurement and the considerable time commitment of formal glucose tolerance testing, which takes two hours to complete and offers no prognostic advantage over the fasting test. According to the current definition, two fasting glucose measurements above 126 mg/dL (7.0 mmol/L) is considered diagnostic for diabetes mellitus.

Patients with fasting glucose levels from 100 to 125 mg/dL (5.6 to 6.9 mmol/L) are considered to have impaired fasting glucose. Patients with plasma glucose at or above 140 mg/dL (7.8 mmol/L), but not over 200 mg/dL (11.1 mmol/L), two hours after a 75 g oral glucose load are considered to have impaired glucose tolerance. Of these two pre-diabetic states, the latter in particular is a major risk factor for progression to full-blown diabetes mellitus as well as cardiovascular disease.

Autoantibodies

The appearance of diabetes-related autoantibodies has been shown to be able to predict the appearance of diabetes type 1 before any hyperglycemia arises, the main ones being islet cell autoantibodies, insulin autoantibodies, autoantibodies targeting the 65 kDa isoform of glutamic acid decarboxylase (GAD) and autoantibodies tergeting the phosphatase-related IA-2 molecule. Per definition, the diagnosis of diabetes type 1 can be made first at the appearance of clinical symptoms and/or signs, but the emergence of autoantibodies may itself be termed *latent autoimmune diabetes*. Not everyone with autoantibodies progress to diabetes type 1, but the risk increases with the number of antibody types, with three to four antibody types giving a risk of progressing to diabetes type 1 of 60%-100%. The time interval from emergence of autoantibodies to frank diabetes type 1 can be a few months in infants and young children, but in some people it may take years - in some cases more than 10 years. Islet cell autoantibodies are detected

by conventional immunofluorescence while the rest are measured with specific radiobinding assays.

Prevention

Type 1 diabetes is not currently preventable. Still, promising therapies are emerging, and it has been suggested that, in the future, diabetes type 1 can be prevented at the latent autoimmune stage, probably by a combination therapy of several methods.

Immunosuppressive drugs

Cyclosporine A, an immunosuppressive agent, has apparently halted destruction of beta cells (on the basis of reduced insulin usage), but its nephrotoxicity and other side effects make it highly inappropriate for long-term use.

Anti-CD3 antibodies, including teplizimab and otelixizumab, have evidence of preserving insulin production (as evidenced by sustained C-peptide production) in newly diagnosed type 1 diabetes patients. A probable mechanism of this effect is preservation of regulatory T cells that suppress activation of the immune system and thereby maintain immune system homeostasis and tolerance to self-antigens. The duration of this effect is still unknown, however.

An anti-CD20 antibody, rituximab, inhibits B cells and has been shown to provoke C-peptide responses three months after diagnosis of type 1 diabetes, but long-term effects of this have not been reported.

Dietary

Some research has suggested that breastfeeding decreased the risk in later life; various other nutritional risk factors are being studied, but no firm evidence has been found. Giving children 2000 IU of Vitamin D during their first year of life is associated with reduced risk of type 1 diabetes, though the causal relationship is obscure.

Children with antibodies to beta cell proteins (i.e. at early stages of an immune reaction to them) but no overt diabetes, and treated with vitamin B_3 (niacin), had less than half the diabetes onset incidence in a 7-year time span as did the general population, and an even lower incidence relative to those with antibodies as above, but who received no vitamin B_3.

T helper cell shift

If a biochemical mechanism can be found that prevents the immune system from attacking beta cells, it may be administered to prevent commencement of diabetes type 1. Several groups are trying to achieve this by causing the activation state of the immune system to change from type 1 T helper cell (Th1) state (“attack” by killer T Cells) to Th2 state (development of new antibodies). This Th1-Th2 shift occurs via a change in the type

of cytokine signaling molecules being released by T-cells. Instead of pro-inflammatory cytokines, the T-cells begin to release cytokines that inhibit inflammation. This phenomenon is commonly known as "acquired immune tolerance".

GAD65 vaccine

Injections with a vaccine containing GAD65, an autoantigen involved in type 1 diabetes, has in clinical trials delayed the destruction of beta cells when treated within six months of diagnosis. Patients treated with the substance showed higher levels of regulatory cytokines, thought to protect the beta cells. Phase III trials are under way in the USA and in Europe. Two prevention studies, where the vaccine is given to persons who have not yet developed diabetes are underway.

Management

Insulin therapy

Type 1 is treated with insulin replacement therapy—either via subcutaneous injection or insulin pump, along with attention to dietary management, typically including carbohydrate tracking, and careful monitoring of blood glucose levels using glucose meters. Today the most common insulins are biosynthetic products produced using genetic recombination techniques; formerly, cattle or pig insulins were used, and even sometimes insulin from fish. Major global suppliers include Eli Lilly and Company, Novo Nordisk, and Sanofi-Aventis. A more recent trend, from several suppliers, is insulin analogs which are slightly modified insulins which have different onset of action times or duration of action times.

Untreated type 1 diabetes commonly leads to coma, often from diabetic ketoacidosis, which is fatal if untreated. Continuous glucose monitors have been developed and marketed which can alert patients to the presence of dangerously high or low blood sugar levels, but technical limitations have limited the impact these devices have had on clinical practice so far.

Pancreas transplantation

In more extreme cases, a pancreas transplant can restore proper glucose regulation. However, the surgery and accompanying immunosuppression required is considered by many physicians to be more dangerous than continued insulin replacement therapy, and is therefore generally only used together with or some time after a kidney transplant. One reason for this is that introducing a new kidney requires taking immunosuppressive drugs such as cyclosporine. Nevertheless this allows the introduction of a new, functioning pancreas to a patient with diabetes without any additional immunosuppressive therapy. However, pancreas transplants alone can be wise in patients with extremely labile type 1 diabetes mellitus.

Islet cell transplantation

Experimental replacement of beta cells (by transplant or from stem cells) is being investigated in several research programs. Islet cell transplantation is expected to be less invasive than a pancreas transplant which is currently the most commonly used approach in humans.

In one variant of this procedure, islet cells are injected into the patient's liver, where they take up residence and begin to produce insulin. The liver is expected to be the most reasonable choice because it is more accessible than the pancreas, and islet cells seem to produce insulin well in that environment. The patient's body, however, will treat the new cells just as it would any other introduction of foreign tissue, unless a method is developed to produce them from the patient's own stem cells or there is an identical twin available who can donate stem cells. The immune system will attack the cells as it would a bacterial infection or a skin graft. Thus, patients now also need to undergo treatment involving immunosuppressants, which reduce immune system activity.

Recent studies have shown that islet cell transplants have progressed to the point that 58% of the patients in one study were insulin independent one year after islet cell transplant. Ideally, it would be best to use islet cells which will not provoke this immune reaction. Scientists in New Zealand with Living Cell Technologies are currently in human trials with Diabecell, placing pig islets within a protective capsule derived of seaweed which enables insulin to flow out and nutrients to flow in while protecting the islets from immune system attack via white blood cells.

Prognosis

Complications of poorly-managed type 1 diabetes mellitus may include cardiovascular disease, diabetic neuropathy, diabetic retinopathy among others. There is some evidence that cardiovascular disease as well as neuropathy may, in fact, have an autoimmune basis as well.

Epidemiology

Type 1 diabetes causes about 5%–10% of all diabetes cases or 11–22 million worldwide. In 2006 it affected 440 thousand children under 14 years of age and was the primary cause of diabetes in those less than 10 years of age. The incidence of type 1 diabetes has been increasing by about 3% per year. Rates vary widely in different countries with a low of 0.1 cases per 100,000 people per year in China and Venezuela to a high of 37 cases per 100,000 people per year in Finland and Sardinia.

Type 1 diabetes was previously known as juvenile diabetes to distinguish it from type 2 diabetes, which generally has a later onset; however, the majority of new-onset type 1 diabetes is seen in adults. Scientific studies that use antibody testing (glutamic acid decarboxylase antibodies (GADA), islet cell antibodies (ICA), and insulinoma-associated autoantibodies (IA-2)) to distinguish between type 1 and type 2 diabetes demonstrate that

most new-onset type 1 diabetes is seen in adults. A 2008 book, *Type 1 Diabetes in Adults: Principles and Practice*, says that adult-onset type 1 autoimmune diabetes is two to three times more common than classic childhood-onset autoimmune diabetes.

Research foundations

The Juvenile Diabetes Research Foundation (JDRF) is the leading charitable funder of research into type 1 diabetes in the UK, Denmark, USA, Canada and Australia. JDRF's mission is to cure type 1 diabetes and its complications through the support of research. Since its founding in 1970, JDRF has contributed more than $1.3 billion to diabetes research, including more than $156 million in FY 2008. In FY 2008, the Foundation funded 1,000 centers, grants and fellowships in 22 countries. In November 2008 JDRF launched an online social network for people with type 1 diabetes: Juvenation.

The International Diabetes Federation is a worldwide alliance of over 160 countries to address diabetes research and treatment. The American Diabetes Association funds type 1 research along with other diabetes-related research (including type 2 diabetes, gestational diabetes and others) that looks at treatments, prevention, and ultimately a cure. Diabetes Australia is involved in promoting research and education in Australia on both type 1 and type 2 diabetes. The Canadian Diabetes Association is involved in educating, researching, and sustaining type 1 diabetes patients in Canada. Pacific Northwest Diabetes Research Institute conducts clinical and basic research on type 1 and type 2 diabetes.

Chapter 5

Diabetes Mellitus Type 2

Diabetes mellitus type 2

Universal blue circle symbol for diabetes

ICD-10	E11.
ICD-9	250.00, 250.02
OMIM	125853
DiseasesDB	3661
MedlinePlus	000313
eMedicine	article/117853
MeSH	D003924

Diabetes mellitus type 2 – formerly **non-insulin-dependent diabetes mellitus (NIDDM)** or **adult-onset diabetes** – is a metabolic disorder that is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency. Diabetes is often initially managed by increasing exercise and dietary modification. As the condition progresses, medications may be needed.

Unlike type 1 diabetes, there is very little tendency toward ketoacidosis though it is not unheard of. One effect that can occur is nonketonic hyperglycemia. Long-term complications from high blood sugar can include increased risk of heart attacks, strokes, amputation, and kidney failure.

Signs and symptoms

The classical symptoms of diabetes are polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased hunger), fatigue and weight loss.

Cause

Type 2 diabetes is due to a combination of lifestyle and genetic factors.

Lifestyle

A number of lifestyle factors are known to be important to the development of type 2 diabetes. In one study, those who had high levels of physical activity, a healthy diet, did not smoke, and consumed alcohol in moderation had an 82% lower rate of diabetes. When a normal weight was included the rate was 89% lower. In this study a healthy diet was defined as one high in fiber, with a high polyunsaturated to saturated fat ratio, and a lower mean glycemic index. Obesity has been found to contribute to approximately 55% of cases of type 2 diabetes, and decreasing consumption of saturated fats and trans fatty acids while replacing them with unsaturated fats may decrease the risk. The increased rate of childhood obesity in between the 1960s and 2000s is believed to have led to the increase in type 2 diabetes in children and adolescents.

Environmental toxins may contribute to recent increases in the rate of type 2 diabetes. A positive correlation has been found between the concentration in the urine of bisphenol A, a constituent of some plastics, and the incidence of type 2 diabetes.

Medical conditions

There are many factors which can potentially give rise to or exacerbate type 2 diabetes. These include obesity, hypertension, elevated cholesterol (combined hyperlipidemia), and with the condition often termed metabolic syndrome (it is also known as Syndrome X, Reavan's syndrome, or CHAOS). Other causes include acromegaly, Cushing's syndrome, thyrotoxicosis, pheochromocytoma, chronic pancreatitis, cancer, and drugs. Additional factors found to increase the risk of type 2 diabetes include aging, high-fat diets and a less active lifestyle.

Subclinical Cushing's syndrome (cortisol excess) may be associated with type 1 diabetes. The percentage of subclinical Cushing's syndrome in the diabetic population is about 9%. Diabetic patients with a pituitary microadenoma can improve insulin sensitivity by removal of these microadenomas.

Hypogonadism is often associated with cortisol excess, and testosterone deficiency is also associated with type 2 diabetes, even if the exact mechanism by which testosterone improve insulin sensitivity is still not known.

Genetics

There is also a strong inheritable genetic connection in type 2 diabetes: having relatives (especially first degree) with type 2 increases risks of developing type 2 diabetes very substantially. In addition, there is also a mutation to the Islet Amyloid Polypeptide gene that results in an earlier onset, more severe, form of diabetes.

About 55 percent of type 2 diabetes patients are obese at diagnosis —chronic obesity leads to increased insulin resistance that can develop into type 2 diabetes, most likely because adipose tissue (especially that in the abdomen around internal organs) is a (recently identified) source of several chemical signals to other tissues (hormones and cytokines).

Other research shows that type 2 diabetes causes obesity as an effect of the changes in metabolism and other deranged cell behavior attendant on insulin resistance.

However, environmental factors (almost certainly diet and weight) play a large part in the development of type 2 diabetes in addition to any genetic component. This can be seen from the adoption of the type 2 diabetes epidemiological pattern in those who have moved to a different environment as compared to the same genetic pool who have not. Immigrants to Western developed countries, for instance, as compared to lower incidence countries of origins.

There is a stronger inheritance pattern for type 2 diabetes. Those with first-degree relatives with type 2 diabetes have a much higher risk of developing type 2 diabetes, increasing with the number of those relatives. Concordance among monozygotic twins is close to 100%, and about 25% of those with the disease have a family history of diabetes. Genes significantly associated with developing type 2 diabetes, include *TCF7L2*, *PPARG*, *FTO*, *KCNJ11*, *NOTCH2*, *WFS1*, *CDKAL1*, *IGF2BP2*, *SLC30A8*, *JAZF1*, and *HHEX*. *KCNJ11* (potassium inwardly rectifying channel, subfamily J, member 11), encodes the islet ATP-sensitive potassium channel Kir6.2, and *TCF7L2* (transcription factor 7–like 2) regulates proglucagon gene expression and thus the production of glucagon-like peptide-1. Moreover, obesity (which is an independent risk factor for type 2 diabetes) is strongly inherited.

Monogenic forms, e.g., MODY, constitute 1–5 % of all cases.

Various hereditary conditions may feature diabetes, for example myotonic dystrophy and Friedreich's ataxia. Wolfram's syndrome is an autosomal recessive neurodegenerative disorder that first becomes evident in childhood. It consists of diabetes insipidus, diabetes mellitus, optic atrophy, and deafness, hence the acronym DIDMOAD.

Gene expression promoted by a diet of fat and glucose as well as high levels of inflammation related cytokines found in the obese results in cells that "produce fewer and smaller mitochondria than is normal," and are thus prone to insulin resistance.

Pathophysiology

Insulin resistance means that body cells do not respond appropriately when insulin is present. Unlike type 1 diabetes mellitus, insulin resistance is generally "post-receptor", meaning it is a problem with the cells that respond to insulin rather than a problem with the production of insulin.

This is a more complex problem than type 1, but is sometimes easier to treat, especially in the early years when insulin is often still being produced internally. Severe complications can result from improperly managed type 2 diabetes, including renal failure, erectile dysfunction, blindness, slow healing wounds (including surgical incisions), and arterial disease, including coronary artery disease. The onset of type 2 diabetes has been most common in middle age and later life, although it is being more frequently seen in adolescents and young adults due to an increase in child obesity and inactivity. A type of diabetes called MODY is increasingly seen in adolescents, but this is classified as a diabetes due to a specific cause and not as type 2 diabetes.

Diabetes mellitus with a known etiology, such as secondary to other diseases, known gene defects, trauma or surgery, or the effects of drugs, is more appropriately called secondary diabetes mellitus or diabetes due to a specific cause. Examples include diabetes mellitus such as MODY or those caused by hemochromatosis, pancreatic insufficiencies, or certain types of medications (e.g., long-term steroid use).

Diagnosis

2006 WHO Diabetes criteria

Condition	**2 hour glucose** mmol/l(mg/dl)	**Fasting glucose** mmol/l(mg/dl)
Normal	<7.8 (<140)	<6.1 (<110)
Impaired fasting glycaemia	<7.8 (<140)	≥ 6.1(≥110) & <7.0(<126)
Impaired glucose tolerance	≥7.8 (≥140)	<7.0 (<126)
Diabetes mellitus	≥11.1 (≥200)	≥7.0 (≥126)

The World Health Organization definition of diabetes is for a single raised glucose reading with symptoms, otherwise raised values on two occasions, of either:

- fasting plasma glucose ≥ 7.0 mmol/l (126 mg/dl)

  or

- With a glucose tolerance test, two hours after the oral dose a plasma glucose ≥ 11.1 mmol/l (200 mg/dl)

Early detection

If a 2-hour postload glucose level of at least 11.1 mmol/L (≥ 200 mg/dL) is used as the reference standard, the fasting plasma glucose > 7.0 mmol/L (126 mg/dL) diagnoses *current* diabetes with:

- sensitivity about 50%
- specificity greater than 95%

A *random* capillary blood glucose > 6.7 mmol/L (120 mg/dL) diagnoses *current* diabetes with:

- sensitivity = 75%
- specificity = 88%

Glycosylated hemoglobin values that are elevated (over 5%), but not in the diabetic range (not over 7.0%) are predictive of *subsequent* clinical diabetes in United States female health professionals. In this study, 177 of 1061 patients with glycosylated hemoglobin value less than 6% became diabetic within 5 years compared to 282 of 26281 patients with a glycosylated hemoglobin value of 6.0% or more. This equates to a glycosylated hemoglobin value of 6.0% or more having:

- sensitivity = 16.7%
- specificity = 98.9%

Screening

No major organization recommends universal screening for diabetes as there is no evidence that such a program would improve outcomes. Screening is recommended by the United States Preventive Services Task Force in adults without symptoms whose blood pressure is greater than 135/80 mmHg. For those whose blood pressure is less the evidence is insufficient to recommend for or against screening. The World Health Organization recommends only testing those groups at high risk.

Prevention

Onset of type 2 diabetes can be delayed or prevented through proper nutrition and regular exercise. Intensive lifestyle measures may reduce the risk by over half. Evidence for the benefit of dietary changes alone however is limited. In those with impaired glucose tolerance diet and exercise and/or metformin or acarbose may decrease the risk of developing diabetes. Lifestyle interventions are more effective than metformin.

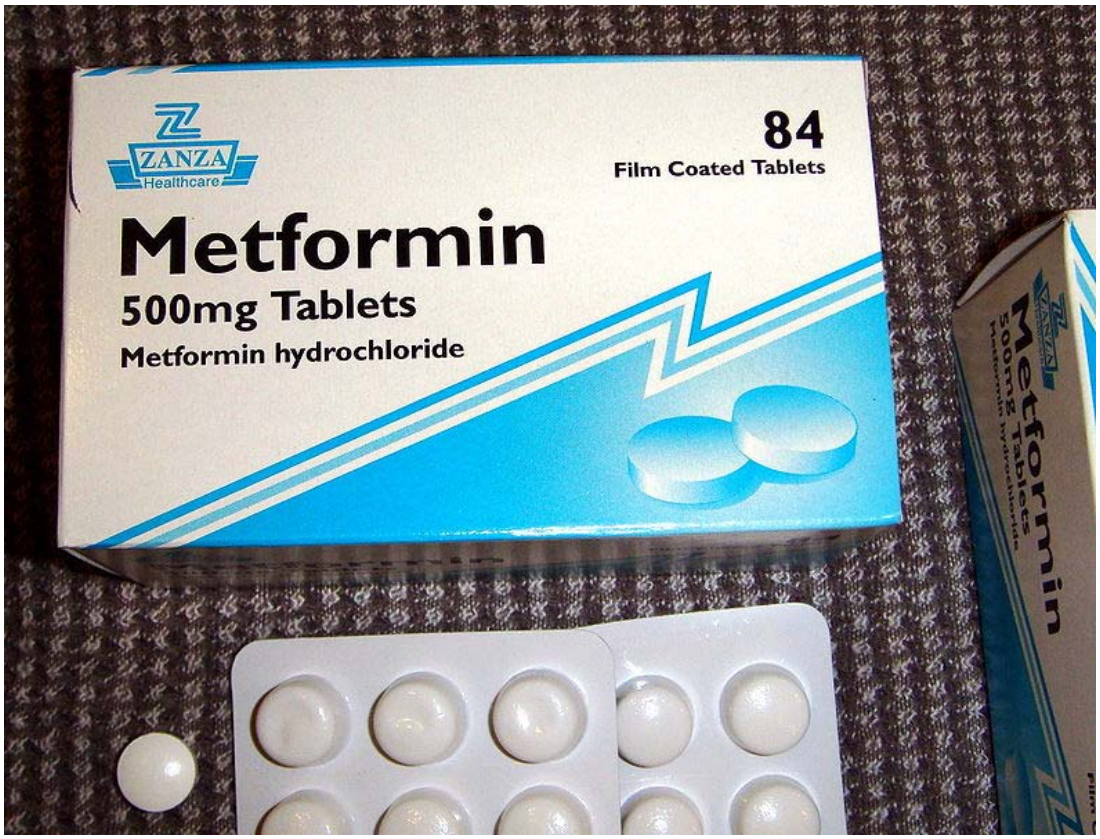
Management

Management of type 2 diabetes focuses on lifestyle interventions, lowering other cardiovascular risk factors, and maintaining blood glucose levels in the normal range. Self-monitoring of blood glucose for people with newly diagnosed type 2 diabetes was recommended by the National Health Services in 2008 however the benefit of self monitoring in those not using multi dose insulin is questionable.

Lifestyle

Aerobic exercise is beneficial in diabetes with the greater the amount of exercise the better the results. It leads to a decrease in HbA1C, improved insulin resistance, and a better V02 max. Resistance training is also useful and the combination of both types of exercise may be most effective. A diabetic diet that promotes weight loss is important. While the best diet type to achieve this is controversial a low glycemic index diet has been found to improve blood sugar control. Culturally appropriate education may help people with type 2 diabetes control their blood sugar levels, for up to six months at least.

Medications



Metformin 500mg tablets

There are several classes of medications available. Metformin is generally recommended first line as there is good evidence that it decreases mortality. Injections of insulin may either be added to oral medication or used alone. Other classes of medications used to treat type 2 diabetes are sulfonylureas, nonsulfonylurea secretagogues, alpha glucosidase inhibitors, and thiazolidinediones.

Insulin

When insulin is used, it is initially usually a long acting formulation and oral medications are continued. Doses of insulin are increased to effect.

The initial insulin regimen are often chosen based on the patient's blood glucose profile. Initially, adding nightly insulin to patients failing oral medications may be best. Nightly insulin combines better with metformin than with sulfonylureas.

When nightly insulin is insufficient, choices include:

- Premixed insulin with a fixed ratio of short and intermediate acting insulin; this tends to be more effective than long acting insulin, but is associated with increased hypoglycemia. Initial total daily dosage of biphasic insulin can be 10 units if the fasting plasma glucose values are less than 180 mg/dl or 12 units when the fasting plasma glucose is above 180 mg/dl". A guide to titrating fixed ratio insulin is available.
- Long acting insulins such as insulin glargine and insulin detemir. A meta-analysis of randomized controlled trials by the Cochrane Collaboration found "only a minor clinical benefit of treatment with long-acting insulin analogues for patients with diabetes mellitus type 2". More recently, a randomized controlled trial found that although long acting insulins were less effective, they were associated with reduced hypoglycemic episodes.

Cardiovascular risk factors

Managing other cardiovascular risk factors including hypertension, high cholesterol, and microalbuminuria improves a persons life expectancy.

Surgery

Gastric Bypass procedures are currently considered an elective procedure with no universally accepted algorithm to decide who should have the surgery. In the diabetic patient, certain types result in 99-100% prevention of insulin resistance and 80-90% clinical resolution or remission of type 2 diabetes. In 1991, the NIH (National Institutes of Health) Consensus Development Conference on Gastrointestinal Surgery for Obesity proposed that the body mass index (BMI) threshold to consider surgery should drop from 40 to 35 in the appropriate patient. More recently, the American Society for Bariatric Surgery (ASBS) and the ASBS Foundation suggested that the BMI threshold be lowered to 30 in the presence of severe co-morbidities. Debate has flourished about the role of

gastric bypass surgery in type 2 diabetics since the publication of The Swedish Obese Subjects Study. The largest prospective series showed a large decrease in the occurrence of type 2 diabetes in the post-gastric bypass patient at both 2 years (odds ratio was 0.14) and at 10 years (odds ratio was 0.25).

A study of 20-years of Greenville (US) gastric bypass patients found that 80% of those with type 2 diabetes before surgery no longer required insulin or oral agents to maintain normal glucose levels. Weight loss occurred rapidly in many people in the study who had had the surgery. The 20% who did not respond to bypass surgery were, typically, those who were older and had had diabetes for over 20 years.

Prognosis

In adults type 2 diabetes is the primary cause of blindness and kidney failure.

Epidemiology

Globally in 2003 it was estimated that there were 150 million people with type 2 diabetes. The incidence varies substantially in different parts of the world, almost certainly because of environmental and lifestyle factors, though these are not known in detail. In the United States there are 23.6 million people (7.8% of the population) with diabetes with 17.9 million being diagnosed, 90% of whom are type 2. With prevalence rates doubling between 1990 and 2005, CDC has characterized the increase as an epidemic. Traditionally considered a disease of adults, type 2 diabetes is increasingly diagnosed in children in parallel to rising obesity rates due to alterations in dietary patterns as well as in life styles during childhood.

Chapter 6

Gestational Diabetes

Gestational diabetes

Universal blue circle symbol for diabetes

ICD-10	O24.
ICD-9	648.8
MedlinePlus	000896
MeSH	D016640

Gestational diabetes (or **gestational diabetes mellitus**, **GDM**) is a condition in which women without previously diagnosed diabetes exhibit high blood glucose levels during pregnancy (especially during third trimester of pregnancy).

Gestational diabetes generally has few symptoms and it is most commonly diagnosed by screening during pregnancy. Diagnostic tests detect inappropriately high levels of glucose in blood samples. Gestational diabetes affects 3-10% of pregnancies, depending on the population studied.

Babies born to mothers with gestational diabetes are typically at increased risk of problems such as being large for gestational age (which may lead to delivery complications), low blood sugar, and jaundice. Gestational diabetes is a treatable condition and women who have adequate control of glucose levels can effectively decrease these risks.

Women with gestational diabetes are at increased risk of developing type 2 diabetes mellitus (or, very rarely, latent autoimmune diabetes or Type 1) after pregnancy, as well as having a higher incidence of pre-eclampsia and Caesarean section; their offspring are prone to developing childhood obesity, with type 2 diabetes later in life. Most patients are treated only with diet modification and moderate exercise but some take anti-diabetic drugs, including insulin.

Classification

Gestational diabetes is formally defined as "any degree of glucose intolerance with onset or first recognition during pregnancy". This definition acknowledges the possibility that patients may have previously undiagnosed diabetes mellitus, or may have developed diabetes coincidentally with pregnancy. Whether symptoms subside after pregnancy is also irrelevant to the diagnosis.

The White classification, named after Priscilla White who pioneered in research on the effect of diabetes types on perinatal outcome, is widely used to assess maternal and fetal risk. It distinguishes between gestational diabetes (type A) and diabetes that existed prior to pregnancy (pregestational diabetes). These two groups are further subdivided according to their associated risks and management.

There are 2 subtypes of gestational diabetes (diabetes which began during pregnancy):

- Type A1: abnormal oral glucose tolerance test (OGTT) but normal blood glucose levels during fasting and 2 hours after meals; diet modification is sufficient to control glucose levels
- Type A2: abnormal OGTT compounded by abnormal glucose levels during fasting and/or after meals; additional therapy with insulin or other medications is required

The second group of diabetes which existed prior to pregnancy is also split up into several subtypes.

Risk Factors

Classical risk factors for developing gestational diabetes are the following:

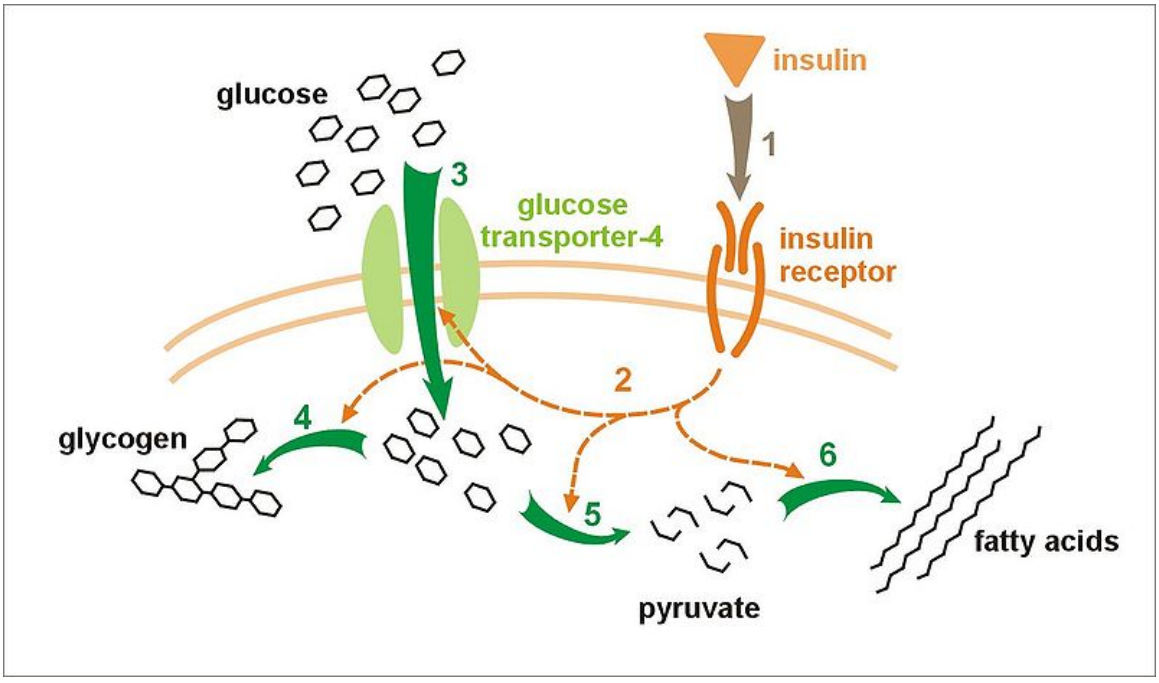
- a previous diagnosis of gestational diabetes or prediabetes, impaired glucose tolerance, or impaired fasting glycaemia
- a family history revealing a first degree relative with type 2 diabetes

- maternal age - a woman's risk factor increases as she gets older (especially for women over 35 years of age)
- ethnic background (those with higher risk factors include African-Americans, Afro-Caribbeans, Native Americans, Hispanics, Pacific Islanders, and people originating from South Asia)
- being overweight, obese or severely obese increases the risk by a factor 2.1, 3.6 and 8.6, respectively.
- a previous pregnancy which resulted in a child with a high birth weight (>90th centile, or >4000 g (8 lbs 12.8 oz))
- previous poor obstetric history

In addition to this, statistics show a double risk of GDM in smokers. Polycystic ovarian syndrome is also a risk factor, although relevant evidence remains controversial. Some studies have looked at more controversial potential risk factors, such as short stature.

About 40-60% of women with GDM have no demonstrable risk factor; for this reason many advocate to screen all women. Typically women with gestational diabetes exhibit no symptoms (another reason for universal screening), but some women may demonstrate increased thirst, increased urination, fatigue, nausea and vomiting, bladder infection, yeast infections and blurred vision.

Pathophysiology



Effect of insulin on glucose uptake and metabolism. Insulin binds to its receptor (1) on the cell membrane which in turn starts many protein activation cascades (2). These include: translocation of Glut-4 transporter to the plasma membrane and influx of glucose (3), glycogen synthesis (4), glycolysis (5) and fatty acid synthesis (6).

The precise mechanisms underlying gestational diabetes remain unknown. The hallmark of GDM is increased insulin resistance. Pregnancy hormones and other factors are thought to interfere with the action of insulin as it binds to the insulin receptor. The interference probably occurs at the level of the cell signaling pathway behind the insulin receptor. Since insulin promotes the entry of glucose into most cells, insulin resistance prevents glucose from entering the cells properly. As a result, glucose remains in the bloodstream, where glucose levels rise. More insulin is needed to overcome this resistance; about 1.5-2.5 times more insulin is produced than in a normal pregnancy.

Insulin resistance is a normal phenomenon emerging in the second trimester of pregnancy, which progresses thereafter to levels seen in non-pregnant patients with type 2 diabetes. It is thought to secure glucose supply to the growing fetus. Women with GDM have an insulin resistance they cannot compensate with increased production in the β-cells of the pancreas. Placental hormones, and to a lesser extent increased fat deposits during pregnancy, seem to mediate insulin resistance during pregnancy. Cortisol and progesterone are the main culprits, but human placental lactogen, prolactin and estradiol contribute too.

It is unclear why some patients are unable to balance insulin needs and develop GDM, however a number of explanations have been given, similar to those in type 2 diabetes: autoimmunity, single gene mutations, obesity, and other mechanisms.

Because glucose travels across the placenta (through diffusion facilitated by GLUT3 carriers), the fetus is exposed to higher glucose levels. This leads to increased fetal levels of insulin (insulin itself cannot cross the placenta). The growth-stimulating effects of insulin can lead to excessive growth and a large body (macrosomia). After birth, the high glucose environment disappears, leaving these newborns with ongoing high insulin production and susceptibility to low blood glucose levels (hypoglycemia).

Screening

2006 WHO Diabetes criteria

Condition	2 hour glucose	Fasting glucose
	mmol/l(mg/dl)	mmol/l(mg/dl)
Normal	<7.8 (<140)	<6.1 (<110)
Impaired fasting glycaemia	<7.8 (<140)	≥ 6.1(≥110) & <7.0(<126)
Impaired glucose tolerance	≥7.8 (≥140)	<7.0 (<126)
Diabetes mellitus	≥11.1 (≥200)	≥7.0 (≥126)

A number of screening and diagnostic tests have been used to look for high levels of glucose in plasma or serum in defined circumstances. One method is a stepwise approach where a suspicious result on a screening test is followed by diagnostic test. Alternatively, a more involved diagnostic test can be used directly at the first antenatal visit in high-risk patients (for example in those with polycystic ovarian syndrome or acanthosis nigricans).

Tests for gestational diabetes

Non-challenge blood glucose tests

- Fasting glucose test
- 2-hour postprandial (after a meal) glucose test
- Random glucose test

Screening glucose challenge test

Oral glucose tolerance test (OGTT)

Non-challenge blood glucose tests involve measuring glucose levels in blood samples without challenging the subject with glucose solutions. A blood glucose level is determined when fasting, 2 hours after a meal, or simply at any random time. In contrast, challenge tests involve drinking a glucose solution and measuring glucose concentration thereafter in the blood; in diabetes, they tend to remain high. The glucose solution has a very sweet taste which some women find unpleasant; sometimes, therefore, artificial flavours are added. Some women may experience nausea during the test, and more so with higher glucose levels.

Pathways

There are different opinions about optimal screening and diagnostic measures, in part due to differences in population risks, cost-effectiveness considerations, and lack of an evidence base to support large national screening programs. The most elaborate regime entails a random blood glucose test during a booking visit, a screening glucose challenge test around 24–28 weeks' gestation, followed by an OGTT if the tests are outside normal limits. If there is a high suspicion, women may be tested earlier.

In the United States, most obstetricians prefer universal screening with a screening glucose challenge test. In the United Kingdom, obstetric units often rely on risk factors and a random blood glucose test. The American Diabetes Association and the Society of Obstetricians and Gynaecologists of Canada recommend routine screening unless the patient is low risk (this means the woman must be younger than 25 years and have a body mass index less than 27, with no personal, ethnic or family risk factors) The Canadian Diabetes Association and the American College of Obstetricians and Gynecologists recommend universal screening. The U.S. Preventive Services Task Force found that there is insufficient evidence to recommend for or against routine screening.

Non-challenge blood glucose tests

When a plasma glucose level is found to be higher than 126 mg/dl (7.0 mmol/l) after fasting, or over 200 mg/dl (11.1 mmol/l) on any occasion, and if this is confirmed on a subsequent day, the diagnosis of GDM is made, and no further testing is required. These

tests are typically performed at the first antenatal visit. They are patient-friendly and inexpensive, but have a lower test performance compared to the other tests, with moderate sensitivity, low specificity and high false positive rates.

Screening glucose challenge test

The screening glucose challenge test (sometimes called the O'Sullivan test) is performed between 24–28 weeks, and can be seen as a simplified version of the oral glucose tolerance test (OGTT). It involves drinking a solution containing 50 grams of glucose, and measuring blood levels 1 hour later.

If the cut-off point is set at 140 mg/dl (7.8 mmol/l), 80% of women with GDM will be detected. If this threshold for further testing is lowered to 130 mg/dl, 90% of GDM cases will be detected, but there will also be more women who will be subjected to a consequent OGTT unnecessarily.

Oral glucose tolerance test

The OGTT should be done in the morning after an overnight fast of between 8 and 14 hours. During the three previous days the subject must have an unrestricted diet (containing at least 150 g carbohydrate per day) and unlimited physical activity. The subject should remain seated during the test and should not smoke throughout the test.

The test involves drinking a solution containing a certain amount of glucose, and drawing blood to measure glucose levels at the start and on set time intervals thereafter.

The diagnostic criteria from the National Diabetes Data Group (NDDG) have been used most often, but some centers rely on the Carpenter and Coustan criteria, which set the cutoff for normal at lower values. Compared with the NDDG criteria, the Carpenter and Coustan criteria lead to a diagnosis of gestational diabetes in 54 percent more pregnant women, with an increased cost and no compelling evidence of improved perinatal outcomes.

The following are the values which the American Diabetes Association considers to be abnormal during the 100 g of glucose OGTT:

- Fasting blood glucose level ≥95 mg/dl (5.33 mmol/L)
- 1 hour blood glucose level ≥180 mg/dl (10 mmol/L)
- 2 hour blood glucose level ≥155 mg/dl (8.6 mmol/L)
- 3 hour blood glucose level ≥140 mg/dl (7.8 mmol/L)

An alternative test uses a 75 g glucose load and measures the blood glucose levels before and after 1 and 2 hours, using the same reference values. This test will identify less women who are at risk, and there is only a weak concordance (agreement rate) between this test and a 3 hour 100 g test.

The glucose values used to detect gestational diabetes were first determined by O'Sullivan and Mahan (1964) in a retrospective cohort study (using a 100 grams of glucose OGTT) designed to detect risk of developing type 2 diabetes in the future. The values were set using whole blood and required two values reaching or exceeding the value to be positive. Subsequent information led to alterations in O'Sullivan's criteria. When methods for blood glucose determination changed from the use of whole blood to venous plasma samples, the criteria for GDM were also changed.

Urinary glucose testing

Women with GDM may have high glucose levels in their urine (glucosuria). Although dipstick testing is widely practiced, it performs poorly, and discontinuing routine dipstick testing has not been shown to cause underdiagnosis where universal screening is performed. Increased glomerular filtration rates during pregnancy contribute to some 50% of women having glucose in their urine on dipstick tests at some point during their pregnancy. The sensitivity of glucosuria for GDM in the first 2 trimesters is only around 10% and the positive predictive value is around 20%.

Management

A kit with a glucose meter and diary used by a woman with gestational diabetes

The goal of treatment is to reduce the risks of GDM for mother and child. Scientific evidence is beginning to show that controlling glucose levels can result in less serious fetal complications (such as macrosomia) and increased maternal quality of life. Unfortunately, treatment of GDM is also accompanied by more infants admitted to neonatal wards and more inductions of labour, with no proven decrease in cesarean section rates or perinatal mortality. These findings are still recent and controversial.

A repeat OGTT should be carried out 2–4 months after delivery, to confirm the diabetes has disappeared. Afterwards, regular screening for type 2 diabetes is advised.

If a diabetic diet or G.I. Diet, exercise, and oral medication are inadequate to control glucose levels, insulin therapy may become necessary.

The development of macrosomia can be evaluated during pregnancy by using sonography. Women who use insulin, with a history of stillbirth, or with hypertension are managed like women with overt diabetes.

Lifestyle

Counselling before pregnancy (for example, about preventive folic acid supplements) and multidisciplinary management are important for good pregnancy outcomes. Most women can manage their GDM with dietary changes and exercise. Self monitoring of blood glucose levels can guide therapy. Some women will need antidiabetic drugs, most commonly insulin therapy.

Any diet needs to provide sufficient calories for pregnancy, typically 2,000 - 2,500 kcal with the exclusion of simple carbohydrates. The main goal of dietary modifications is to avoid peaks in blood sugar levels. This can be done by spreading carbohydrate intake over meals and snacks throughout the day, and using slow-release carbohydrate sources—known as the G.I. Diet. Since insulin resistance is highest in mornings, breakfast carbohydrates need to be restricted more.

Regular moderately intense physical exercise is advised, although there is no consensus on the specific structure of exercise programs for GDM.

Self monitoring can be accomplished using a handheld capillary glucose dosage system. Compliance with these glucometer systems can be low. Target ranges advised by the Australasian Diabetes in Pregnancy Society are as follows:

- fasting capillary blood glucose levels <5.5 mmol/L
- 1 hour postprandial capillary blood glucose levels <8.0 mmol/L
- 2 hour postprandial blood glucose levels <6.7 mmol/L

Regular blood samples can be used to determine HbA1c levels, which give an idea of glucose control over a longer time period.

Research suggests a possible benefit of breastfeeding to reduce the risk of diabetes and related risks for both mother and child.

Medication

If monitoring reveals failing control of glucose levels with these measures, or if there is evidence of complications like excessive fetal growth, treatment with insulin might become necessary. The most common therapeutic regime involves premeal fast-acting insulin to blunt sharp glucose rises after meals. Care needs to be taken to avoid low blood sugar levels (hypoglycemia) due to excessive insulin injections. Insulin therapy can be normal or very tight; more injections can result in better control but requires more effort, and there is no consensus that it has large benefits.

There is some evidence that certain oral glycemic agents might be safe in pregnancy, or at least, are significantly less dangerous to the developing fetus than poorly controlled diabetes. Glyburide, a second generation sulfonylurea, has been shown to be an effective alternative to insulin therapy. In one study, 4% of women needed supplemental insulin to reach blood sugar targets. Metformin has shown promising results, with its oral format being much more popular than insulin injections. Treatment of polycystic ovarian syndrome with metformin during pregnancy has been noted to decrease GDM levels. A recent randomized controlled trial of metformin versus insulin showed that women preferred metformin tablets to insulin injections, and that metformin is safe and equally effective as insulin. Severe neonatal hypoglycemia was less common in insulin-treated women, but preterm delivery was more common. Almost half of patients did not reach sufficient control with metformin alone and needed supplemental therapy with insulin; compared to those treated with insulin alone, they required less insulin, and they gained less weight. With no long-term studies into children of women treated with the drug, here remains a possibility of long-term complications from metformin therapy, although follow-up at the age of 18 months of children born to women with polycystic ovarian syndrome and treated with metformin revealed no developmental abnormalities.

Prognosis

Gestational diabetes generally resolves once the baby is born. Based on different studies, the chances of developing GDM in a second pregnancy are between 30 and 84%, depending on ethnic background. A second pregnancy within 1 year of the previous pregnancy has a high rate of recurrence.

Women diagnosed with gestational diabetes have an increased risk of developing diabetes mellitus in the future. The risk is highest in women who needed insulin treatment, had antibodies associated with diabetes (such as antibodies against glutamate decarboxylase, islet cell antibodies and/or insulinoma antigen-2), women with more than two previous pregnancies, and women who were obese (in order of importance). Women requiring insulin to manage gestational diabetes have a 50% risk of developing diabetes within the next five years. Depending on the population studied, the diagnostic criteria and the length of follow-up, the risk can vary enormously. The risk appears to be highest

in the first 5 years, reaching a plateau thereafter. One of the longest studies followed a group of women from Boston, Massachusetts; half of them developed diabetes after 6 years, and more than 70% had diabetes after 28 years. In a retrospective study in Navajo women, the risk of diabetes after GDM was estimated to be 50 to 70% after 11 years. Another study found a risk of diabetes after GDM of more than 25% after 15 years. In populations with a low risk for type 2 diabetes, in lean subjects and in patients with auto-antibodies, there is a higher rate of women developing type 1 diabetes.

Children of women with GDM have an increased risk for childhood and adult obesity and an increased risk of glucose intolerance and type 2 diabetes later in life. This risk relates to increased maternal glucose values. It is currently unclear how much genetic susceptibility and environmental factors each contribute to this risk, and if treatment of GDM can influence this outcome.

There are scarce statistical data on the risk of other conditions in women with GDM; in the Jerusalem Perinatal study, 410 out of 37962 patients were reported to have GDM, and there was a tendency towards more breast and pancreatic cancer, but more research is needed to confirm this finding.

Complications

GDM poses a risk to mother and child. This risk is largely related to high blood glucose levels and its consequences. The risk increases with higher blood glucose levels. Treatment resulting in better control of these levels can reduce some of the risks of GDM considerably.

The two main risks GDM imposes on the baby are growth abnormalities and chemical imbalances after birth, which may require admission to a neonatal intensive care unit. Infants born to mothers with GDM are at risk of being both large for gestational age (macrosomic) and small for gestational age. Macrosomia in turn increases the risk of instrumental deliveries (e.g. forceps, ventouse and caesarean section) or problems during vaginal delivery (such as shoulder dystocia). Macrosomia may affect 12% of normal women compared to 20% of patients with GDM. However, the evidence for each of these complications is not equally strong; in the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study for example, there was an increased risk for babies to be large but not small for gestational age. Research into complications for GDM is difficult because of the many confounding factors (such as obesity). Labelling a woman as having GDM may in itself increase the risk of having a caesarean section.

Neonates are also at an increased risk of low blood glucose (hypoglycemia), jaundice, high red blood cell mass (polycythemia) and low blood calcium (hypocalcemia) and magnesium (hypomagnesemia). GDM also interferes with maturation, causing dysmature babies prone to respiratory distress syndrome due to incomplete lung maturation and impaired surfactant synthesis.

Unlike pre-gestational diabetes, gestational diabetes has not been clearly shown to be an independent risk factor for birth defects. Birth defects usually originate sometime during the first trimester (before the 13th week) of pregnancy, whereas GDM gradually develops and is least pronounced during the first trimester. Studies have shown that the offspring of women with GDM are at a higher risk for congenital malformations. A large case-control study found that gestational diabetes was linked with a limited group of birth defects, and that this association was generally limited to women with a higher body mass index ($\geq 25\ kg/m^2$). It is difficult to make sure that this is not partially due to the inclusion of women with pre-existent type 2 diabetes who were not diagnosed before pregnancy.

Because of conflicting studies, it is unclear at the moment whether women with GDM have a higher risk of preeclampsia. In the HAPO study, the risk of preeclampsia was between 13% and 37% higher, although not all possible confounding factors were corrected.

Epidemiology

Gestational diabetes affects 3-10% of pregnancies, depending on the population studied.

Chapter 7

Latent Autoimmune Diabetes

Latent Autoimmune Diabetes of Adults (LADA), also known as, **Diabetes Type 1.5**, is a term coined by Tuomi et al. in 1993 (Diabetes 42:359-362) to describe slow-onset Type 1 autoimmune diabetes in adults. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (Diabetes Care, Volume 30, Supplement 1, January 2007) does not recognize the term LADA; rather, the Expert Committee includes LADA in the definition of Type 1 autoimmune diabetes ("Type 1 diabetes results from a cellular-mediated autoimmune destruction of the beta-cells of the pancreas. In Type 1 diabetes, the rate of beta-cell destruction is quite variable, being rapid in some individuals (mainly infants and children) and slow in others (mainly adults).") The National Institutes of Health (NIDDK) defines LADA as "a condition in which Type 1 diabetes develops in adults." LADA is a genetically-linked, hereditary autoimmune disorder that results in the body mistaking the pancreas as foreign and responding by attacking and destroying the insulin-producing beta islet cells of the pancreas. Simply stated, autoimmune disorders, including LADA, are an "allergy to self."

Adults with LADA are frequently initially misdiagnosed as having Type 2 diabetes, based on age, not etiology. In a recent survey conducted by Australia's Type 1 Diabetes Network, one third of all Australians with type 1 diabetes reported being initially misdiagnosed as having the more common type 2 diabetes.

Other names for LADA

LADA may be diagnosed using any of the following terms:

- latent autoimmune diabetes of adulthood
- late-onset autoimmune diabetes of adulthood
- latent autoimmune diabetes of aging
- slow onset type 1 diabetes, or
- type 1.5 (type one-and-a-half) diabetes

Diagnosing latent autoimmune diabetes

It is estimated that 20% of persons diagnosed as having non-obesity-related type 2 diabetes may actually have LADA. Islet cell, insulin, and GAD antibodies testing should

be performed on all adults who are not obese that appear to present with type 2 diabetes. Not all people having LADA are thin or skinny, however—there are plus-sized individuals carrying LADA but not getting accurately diagnosed because of their weight. These individuals are more often denied insulin by their health care physicians, considering people who were diagnosed with or have type 2 diabetes are given those treatments by diabetes specialists or their physicians extremely often. Moreover, it is now becoming evident that autoimmune diabetes may be highly underdiagnosed in many individuals who have diabetes, and that the body mass index levels may have rather limited use in connections with latent autoimmune diabetes. Also, many physicians or diabetes specialists don't recognize LADA or probably don't know the condition actually exists, and so LADA is misdiagnosed as or mistaken for Type 2 diabetes highly often.

Diagnostic tests include:

C-peptide (also known as insulin C-peptide, connecting peptide)

This test measures residual beta cell function by determining the level of insulin secretion (C-peptide). Persons with LADA typically have low, although sometimes moderate, levels of C-peptide as the disease progresses. Patients with insulin resistance or type 2 diabetes are more likely to, but will not always, have high levels of C-peptide due to an over production of insulin.

Diabetes mellitus autoantibody panel

Glutamic acid decarboxylase (GAD) autoantibodies, radioimmunoassay (RIA) and insulin antibodies, radioimmunoassay, RIA.

Glutamic acid decarboxylase antibodies are commonly found in diabetes mellitus type 1.

Islet Cell Antibodies (ICA) tests

Islet Cell IgG Cytoplasmic Autoantibodies, IFA; Islet Cell Complement Fixing Autoantibodies, Indirect Fluorescent Antibody (IFA); Islet Cell Autoantibodies Evaluation; Islet Cell Complement Fixing Autoantibodies - Aids in a differential diagnosis between LADA and type 2 diabetes. Persons with LADA often test positive for ICA, whereas type 2 diabetics only seldom do.

Glutamic Acid Decarboxylase (GAD) Antibodies tests

Microplate ELISA: Anti-GAD, Anti-IA2, Anti-GAD/IA2 Pool - In addition to being useful in making an early diagnosis for type 1 diabetes mellitus, GAD antibodies tests are used for differential diagnosis between LADA and type 2 diabetes and may also be used for differential diagnosis of gestational diabetes, risk prediction in immediate family members for type 1, as well as a tool to monitor prognosis of the clinical progression of type 1 diabetes.

Insulin Antibodies (IAA)tests

RIA: Anti-GAD, Anti-IA2, Anti-Insulin; Insulin Antibodies - These tests are also used in early diagnosis for type 1 diabetes mellitus, and for differential diagnosis between LADA and type 2 diabetes, as well as for differential diagnosis of gestational diabetes, risk prediction in immediate family members for type 1, and to monitor prognosis of the clinical progression of type 1 diabetes. Persons with LADA may test positive for insulin antibodies; persons with type 2, however, rarely do.

Other characteristics of LADA that may aid in differential diagnosis include:

- Onset usually at 25 years of age or older
- Initially mimics non-obese type 2 diabetes (patients are usually thin or of normal weight, although some may be overweight to minimally obese)
- Oftentimes, but not always, a lack of family history for T2DM (family history for type 2 diabetes is sometimes involved regarding a latent autoimmune diabetic adult)
- Persons with LADA are insulin resistant like, but at prevalence levels less than, Type 2
- Human leukocyte antigen (HLA) genes associated with type 1 diabetes are seen in LADA but not in type 2 diabetes
- Although some people having type 2 diabetes may inject insulin, this only rarely happens; in contrast, people with LADA require insulin injections around three to 12 years after so called type 2 diabetes diagnoses

Prevalence

It is estimated that approximately 20% of all persons diagnosed with type 2 diabetes might actually have LADA. This number accounts for an estimated 5%-10% of the total diabetes population in the U.S. or, as many as 3.5 million persons with LADA. Actual numbers, however, may be higher and more severe than estimates indicate.

Treatment

LADA often does not require insulin at the time of diagnosis and may even be managed with changes in lifestyle in its early stages such as exercise, eating right, and, if optional, weight loss. However, some clinicians believe that insulin should be started at onset or as soon as possible, rather than using sulfonylureas or other diabetes pills for initial treatment. Moreover, it is not clear whether early insulin therapy is of benefit to the remaining beta islet cells.

Initially, a person with LADA may respond to oral diabetes medications, eating right and lifestyle changes, although beta cells continue to be destroyed and LADA patients should be closely monitored. Some studies have demonstrated that the use of sulfonylureas and the insulin-sensitizing drug metformin, may increase the risk of severe metabolic disorder in persons with LADA. When blood glucose can no longer be managed through lifestyle and medications, daily insulin injections will be required.

80% of persons initially diagnosed with type 2 but test positive for GAD (an indication of LADA) progress to insulin dependency within 6 years (some sources say between 3–12 years after diagnosis). Those who test positive for both GAD and IA2, however, will progress more rapidly to insulin dependence.

Living with any chronic illness is stressful, and patients with diabetes, let alone LADA, may be more prone to depression and eating disorders as a result. Counseling, therapy, and participation in support groups can play an important and positive role in the lives of persons with LADA.

Part of diabetes therapy should include patient education about diet, exercise, stress management, and handling their diabetes on "sick" days. Patients need to understand how to manage their diabetes, as well as how to recognize, treat, and prevent hypoglycemia (low blood sugar) and hyperglycemia (high blood sugar) and how to give injections of insulin and glucagon. Blood glucose levels should be checked not less than 3-4 times per day when a patient is insulin dependent and, often, at least once during the night.

Hypoglycemia

Hypoglycemia (low blood sugar) presents an immediate and life-threatening danger. Any reading 70 mg/dL (3.9 mmol/L) or below, for a person with diabetes, classifies as "low."

If the blood glucose falls too low a person can become disoriented and unable to swallow. Without being able to ingest a fast-acting sugar they may lose consciousness. If left untreated, hypoglycemia can lead to seizures, diabetic coma and death. Onset of hypoglycemia is often, albeit not always, rapid, and may be attributed to many things including too much insulin (insulin shock), not eating enough, heavy exercise, excitement, certain medications, or a combination of factors.

Because of the potential danger associated with hypoglycemia, persons using insulin should carry a glucagon kit, fast-acting food sugars, and medical identification with them at all times. At least one family member or friend should be instructed on glucagon administration as the patient is likely to be unable to inject themselves.

Hyperglycemia

Hyperglycemia (high blood glucose levels) occurs when too much food is eaten for insulin that was taken, not enough insulin, stress, dehydration, or illness are present. Hyperglycemia, if untreated, can lead to a deadly state called diabetic ketoacidosis

(DKA). If insufficient insulin is present the body cannot use blood glucose as energy, and a combination of things happen, one of which is the body turning to fat stores for energy. Burning of fat causes a ketonic state that may result in an excess of ketones. Persons with high blood glucose levels should use a test strip to check their urine for ketones anytime their glucose levels are 240 mg/dL (13.3 mmol/L) or higher. Patients should call their doctor if ketones measure in the moderate-to-high range as DKA may require hospitalization.

A person in DKA requires immediate medical attention and should not attempt to simply administer more insulin independent of a physician's recommendation. Doing so (self-treating) could lead to serious health risks, even death. DKA can lead to heart failure, cerebral edema, coma, and death.

Long-term complications

The long-term complications of LADA are the same as for those with type 1 (formerly juvenile diabetes) and with type 2. According to one major study, the Diabetes Control and Complications Trial (DCCT), the risk of long-term problems are directly related to how well the blood glucose levels are managed. The American Diabetes Association recommends LADA patients strive for a HbA1c test of 7.0 or lower.

Uncontrolled diabetes of all types results in high blood glucose levels (hyperglycemia) which over time may cause diabetic neuropathy, diabetic retinopathy, eye trouble, kidney failure, heart disease, high blood pressure, stroke, peripheral arterial disease (PAD), chronic infections and wounds that may not heal, erectile and other urological dysfunction, gastroparesis (delayed emptying of stomach contents), gangrene, blindness, amputation, lactic acidosis, diabetic ketoacidosis (DKA).

Prognosis

According to one study—"Similar as in prediabetic relatives of type 1 diabetic patients the risk for beta cell failure in adult 'type 2 diabetic' patients increases with the number of antibodies positive."

Eventually, the latent autoimmune diabetic adult will become dependent upon injecting insulin in order to maintain glucose control. They will require daily injection of insulin and need to be diligent in following their diabetes care plan provided by their physician.

Diabetes, including latent autoimmune diabetes of adults, is a chronic illness that can have devastating complications. However, it is possible for most persons with diabetes to actively participate in their daily health care needs and dramatically reduce the risk of diabetes complications.

Patient education, motivation, and state of mental health all play an important role in how well a person with LADA will be able to manage their disease.

Comparison between LADA, type 1 diabetes and type 2 diabetes

LADA is slow-onset Type 1 autoimmune diabetes in adulthood (NIDDK - National Institute of Diabetes and Digestive and Kidney Diseases).

- Onset: Type 1 diabetes onsets rapidly and at a younger age than does LADA.
- Family history: There is often a family history of autoimmune conditions (for example, rheumatoid arthritis, thyroid diseases, etc.). Furthermore, there is controversy about whether or not people with LADA have a family history of T2DM.
- Antibodies: Persons with type 1 diabetes and LADA usually test positive for certain (same) antibodies (GAD, ICA, IA-2) that are not present in type 2 diabetes. Moreover, there are also TCF7L2 genes associated with Type 2 diabetes involved in latent autoimmune diabetes of adults.
- GAD antibodies: Persons with LADA usually test positive for GAD antibodies, whereas in type 1 diabetes these antibodies are more commonly seen in adults rather than in children.
- Lifestyle and excess weight: People with LADA typically have a normal BMI or may be underweight due to weight loss prior to diagnosis. But some people with LADA may be overweight to mildly obese. LADA (Type 1 diabetes) is an autoimmune disease that cannot be prevented.
- Prognosis: About 80% of all persons initially diagnosed with type 2, who also have GAD antibodies, will become insulin dependent within 3 to 12 years (according to differing LADA sources). Those with both GAD and IA2 antibodies, however, will become insulin dependent sooner. LADA occurs slowly, but progresses towards insulin dependency.
- Treatment: Although LADA may appear to initially respond to similar treatment (lifestyle and medications, sometimes weight loss if needed) as type 2 diabetes, it will not halt or slow the progression of beta cell destruction, and people with LADA will eventually become insulin dependent.

Chapter 8

Maturity Onset Diabetes of the Young

Maturity onset diabetes of the young	
OMIM	606391
DiseasesDB	8330
MeSH	D003924

Maturity onset diabetes of the young (**MODY**) refers to any of several hereditary forms of diabetes caused by mutations in an autosomal dominant gene (sex independent, i.e. inherited from any of the parents) disrupting insulin production. MODY is often referred to as "**monogenic diabetes**" to distinguish it from the more common types of diabetes (especially type 1 and type 2), which involve more complex combinations of causes involving multiple genes (i.e., "polygenic") and environmental factors. MODY 2 and MODY 3 are the most common forms. The severity of the different types varies considerably, but most commonly MODY acts like a very mild version of type 1 diabetes, with continued partial insulin production and normal insulin sensitivity. MODY is not type 2 diabetes in a young person, as might erroneously be inferred from the name.

History of the concept and treatment of MODY

The term MODY dates back to 1964, when diabetes mellitus was considered to have two main forms: juvenile-onset and maturity-onset, which roughly corresponded to what we now call type 1 and type 2. MODY was originally applied to any child or young adult who had persistent, asymptomatic hyperglycemia without progression to diabetic ketosis or ketoacidosis. In retrospect we can now recognize that this category covered a heterogeneous collection of disorders which included cases of dominantly inherited diabetes, as well as cases of what we would now call type 2 diabetes occurring in childhood or adolescence, and a few even rarer types of hyperglycemia (e.g., mitochondrial diabetes or mutant insulin). Many of these patients were treated with sulfonylureas with varying degrees of success.

By the 1990s, as the understanding of the pathophysiology of diabetes has improved, the concept and usage of "MODY" have become refined and narrower. It is now used as a

synonym for dominantly inherited, monogenic defects of insulin secretion occurring at any age, and no longer includes any forms of type 2 diabetes.

Signs, symptoms and differential diagnosis

There are two general types of clinical presentation.

- Some forms of MODY produce significant hyperglycemia and the typical signs and symptoms of diabetes: increased thirst and urination (polydipsia and polyuria).
- In contrast, however, many people with MODY have no signs or symptoms and are diagnosed by either accident, when a high glucose is discovered during testing for other reasons, or screening of relatives of a person discovered to have diabetes. Discovery of mild hyperglycemia during a routine glucose tolerance test for pregnancy is particularly characteristic.

MODY cases may make up as many as 5% of presumed type 1 and type 2 diabetes cases in a large clinic population. While the goals of diabetes management are the same no matter what type, there are two primary advantages of confirming a diagnosis of MODY.

- Firstly, insulin may not be necessary and it may be possible to switch a person from insulin injections to oral agents without loss of glycemic control.
- Secondly, it may prompt screening of relatives and so help identify other cases in family members.

As it occurs infrequently, many cases of MODY are initially assumed to be more common forms of diabetes: type 1 if the patient is young and not overweight, type 2 if the patient is overweight, or gestational diabetes if the patient is pregnant. Standard diabetes treatments (insulin for type 1 and gestational diabetes, and oral hypoglycemic agents for type 2) are often initiated before the doctor suspects a more unusual form of diabetes.

Treatment

In some forms of MODY, standard treatment is appropriate, though exceptions occur:

- In MODY2, oral agents are relatively ineffective and insulin is unnecessary.
- In MODY1 and MODY3, insulin may be more effective than drugs to increase insulin sensitivity.
- Sulfonylureas are effective in the K_{ATP} channel forms of neonatal-onset diabetes.

Presentation of MODY

The following characteristics suggest the possibility of a diagnosis of MODY in hyperglycemic and diabetic patients:

- Mild to moderate hyperglycemia (typically 130–250 mg/dl, or 7-14 mM) discovered before 30 years of age. However, anyone under 50 can develop MODY.
- A first degree relative with a similar degree of diabetes.
- Absence of positive antibodies or other autoimmunity (e.g., thyroiditis) in patient and family.
- Persistence of a low insulin requirement (e.g., less than 0.5 u/kg/day) past the usual "honeymoon" period.
- Absence of obesity (although overweight or obese people can get MODY), or other problems associated with type 2 diabetes or metabolic syndrome (e.g. hypertension, hyperlipidemia, polycystic ovary syndrome).
- Insulin resistance very rarely happens.
- Cystic kidney disease in patient or close relatives.
- Non-transient neonatal diabetes, or apparent type 1 diabetes with onset before 6 months of age.

The diagnosis of MODY is confirmed by specific gene testing, now available through several commercial laboratories.

Pathophysiology

The recognised forms of MODY are all due to ineffective insulin production or release by pancreatic β-cells. Several of the defects are mutations of transcription factor genes. One form is due to mutations of the glucokinase gene. For each form of MODY, multiple specific mutations involving different amino acid substitutions have been discovered. In some cases, there are significant differences in the activity of the mutant gene product that contribute to variations in the clinical features of the diabetes (such as degree of insulin deficiency or age of onset).

Genetics

Some sources make a distinction between two different forms of monogenetic diabetes: MODY and neonatal diabetes. However, they have much in common, and are often studied together.

Heterozygous

MODY is inherited in an autosomal dominant fashion, and most patients therefore have other members of the family with diabetes; penetrance differs between the types (from 40% to 90%).

Type	OMIM	Gene/protein	Description
MODY 1	125850	hepatocyte nuclear factor 4α	due to a loss-of-function mutation in the HNF4α gene
MODY 2	125851	glucokinase	due to any of several mutations in the *GCK* gene
MODY 3	600496	hepatocyte nuclear factor 1α	mutations of the HNF1α; gene, a homeobox gene
MODY 4	606392	insulin promoter factor-1	mutations of the IPF1 homeobox (Pdx1) gene
MODY 5	137920	hepatocyte nuclear factor 1β	one of the less common forms of MODY, with some distinctive clinical features, including atrophy of the pancreas and several forms of renal disease.
MODY 6	606394	neurogenic differentiation 1	mutations of the gene for the transcription factor referred to as neurogenic differentiation 1.
MODY 7	610508	Kruppel-like factor 11	KLF11 has been associated with a form of diabetes that has been characterized as "MODY7" by OMIM.
MODY 8	609812	Bile salt dependent lipase	CEL has been associated with a form of diabetes that has been characterized as "MODY8" by OMIM.
MODY 9	612225	PAX4	
Permanent neonatal diabetes mellitus	606176	KCNJ11	A newly identified and potentially treatable form of monogenic diabetes is the neonatal diabetes caused by activating mutations of the ABCC8 or *KCNJ11* gene.
Transient neonatal diabetes mellitus	601410 610374 610582	ABCC8	Some forms of neonatal-onset diabetes are not permanent.

Homozygous

By definition, the forms of MODY are autosomal dominant, requiring only one abnormal gene to produce the disease; the severity of the disease is moderated by the presence of a second, normal allele which presumably functions normally. However, conditions involving people carrying two abnormal alleles have been identified. Unsurprisingly, combined (homozygous) defects of these genes are both much rarer and much more severe in their effects.

- MODY2: Homozygous glucokinase deficiency causes severe congenital insulin deficiency resulting in persistent neonatal diabetes mellitus. About 6 cases have been reported worldwide. All have required insulin treatment from shortly after birth. The condition does not seem to improve with age.

- MODY4: Homozygous IPF1 results in failure of the pancreas to form. Congenital absence of the pancreas, termed pancreatic agenesis, involves deficiency of both endocrine and exocrine functions of the pancreas.

Homozygous mutations in the other forms have not yet been described. Those mutations for which a homozygous form has not been described may be extremely rare, or may result in clinical problems not yet recognized as connected to the monogenic disorder, or may be lethal for a fetus and not result in a viable child.

Management

Unfortunately, chronic hyperglycemia of any cause can eventually cause blood vessel damage and the microvascular complications of diabetes. The principal treatment goals for people with MODY — keeping the blood sugars as close to normal as possible ("good glycemic control"), while minimizing other vascular risk factors — are the same for all known forms of diabetes.

Tools available for management are also those available for all forms of diabetes: blood testing, changes in diet, physical exercise, oral hypoglycemic agents, and insulin injections. In many cases these goals can be achieved more easily with MODY than with ordinary types 1 and 2 diabetes. Some people with MODY may require insulin injections to achieve the same glycemic control that another person may attain with careful eating or an oral medication.

When oral hypoglycemic agents are used in MODY, the sulfonylureas remain the oral medication of first resort. Patients with MODY less often suffer from obesity and insulin resistance than those with ordinary type 2 diabetes (for whom insulin sensitizers like metformin or the thiazolidinediones are often preferred over the sulfonylureas).

Incidence

According to data from Saxony, Germany, MODY was responsible for 2.4% of diabetes incidence in children aged less than 15 years.

Chapter 9

Glycated Hemoglobin and Glucose Tolerance Test

Glycated hemoglobin

Glycated hemoglobin (**glycosylated hemoglobin**, *hemoglobin A1c, HbA_{1c}, A1C*, or *Hb_{1c}*; sometimes also **HbA1c**) is a form of hemoglobin used primarily to identify the average plasma glucose concentration over prolonged periods of time. It is formed in a non-enzymatic glycation pathway by hemoglobin's exposure to plasma glucose. Normal levels of glucose produce a normal amount of glycated hemoglobin. As the average amount of plasma glucose increases, the fraction of glycated hemoglobin increases in a predictable way. This serves as a marker for average blood glucose levels over the previous months prior to the measurement.

The 2010 American Diabetes Association Standards of Medical Care in Diabetes added the A1c $\geq$ 6.5% as another criterion for the diagnosis of diabetes, but this is controversial and has not been universally adopted.

In diabetes mellitus, higher amounts of glycated hemoglobin, indicating poorer control of blood glucose levels, have been associated with cardiovascular disease, nephropathy, and retinopathy. Monitoring the HbA_{1c} in type-1 diabetic patients may improve treatment.

History

Hemoglobin A1c was first separated from other forms of hemoglobin by Huisman and Meyering in 1958 using a chromatographic column. It was first characterized as a glycoprotein by Bookchin and Gallop in 1968. Its increase in diabetes was first described in 1969 by Samuel Rahbar et. al. The reactions leading to its formation were characterized by Bunn and his co-workers in 1975. The use of hemoglobin A1c for monitoring the degree of control of glucose metabolism in diabetic patients was proposed in 1976 by Anthony Cerami, Ronald Koenig and coworkers.

Underlying principle

In the normal 120-day lifespan of the red blood cell, glucose molecules react with hemoglobin, forming glycated hemoglobin. In individuals with poorly controlled diabetes, the quantities of these glycated hemoglobins are much higher than in healthy people.

Once a hemoglobin molecule is glycated, it remains that way. A buildup of glycated hemoglobin within the red cell, therefore, reflects the average level of glucose to which the cell has been exposed during its life-cycle. Measuring glycated hemoglobin assesses the effectiveness of therapy by monitoring long-term serum glucose regulation. The HbA_{1c} level is proportional to average blood glucose concentration over the previous four weeks to three months. Some researchers state that the major proportion of its value is related to a rather shorter period of two to four weeks.

The 2010 American Diabetes Association Standards of Medical Care in Diabetes added the A1c $\geq$ 6.5% as another criterion for the diagnosis of diabetes, but this is controversial and has not been universally adopted.

Measuring A1C

There are a number of techniques used to measure A1C.

Laboratories use:

- high-performance liquid chromatography (HPLC): The HbA1c result is calculated as a ratio to total haemoglobin by using a chromatogram.
- immunoassay

Point of care (e.g. doctor's surgery) devices use:

- immunoassay
- boronate affinity chromatography

In the United States, POC A1C tests are certified by the National Glycohemoglobin Standardization Program (NGSP) to standardise them against the results of the 1993 Diabetes Control and Complications Trial (DCCT).

Switch to IFCC units

The American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD) and International Diabetes Federation (IDF) have agreed that, in the future, HbA_{1c} is to be reported in the International Federation of Clinical Chemistry (IFCC) units. IFCC reporting was introduced in Europe except for the UK in 2003, and the UK has as of 1 June 2009 introduced dual reporting until 1 June 2011.

Conversion between the units is by the following equation: IFCC-HbA_{1c} (mmol/mol) = [DCCT-HbA_{1c} (%) - 2.15] × 10.929

DCCT- HbA_{1c} (%)	**IFCC-HbA_{1c}** (mmol/mol)
4.0	20
5.0	31
6.0	42
6.5	48
7.0	53
7.5	59
8.0	64
9.0	75
10.0	86

Interpretation of results

Laboratory results may differ depending on the analytical technique, the age of the subject, and biological variation among individuals. Two individuals with the same average blood sugar can have A1C values that differ by as much as 3 percentage points. Results can be unreliable in many circumstances, such as after blood loss, for example, after surgery, blood transfusions, anemia, or high erythrocyte turnover; in the presence of chronic renal or liver disease; after administration of high-dose vitamin C; or erythropoetin treatment. In general, the reference range (that found in healthy persons), is about 4%–5.9%.

Higher levels of HbA_{1c} are found in people with persistently elevated blood sugar, as in diabetes mellitus. While diabetic patient treatment goals vary, many include a target range of HbA_{1c} values. A diabetic person with good glucose control has a HbA_{1c} level that is close to or within the reference range. **The International Diabetes Federation and American College of Endocrinology recommend HbA_{1c} values below 6.5%, while American Diabetes Association recommends that the HbA_{1c} be below 7.0% for most patients**. Recent results from large trials suggest that a target below 7% may be excessive: Below 7% the health benefits of reduced A1C become smaller, and the intensive glycemic control required to reach this level leads to an increased rate of dangerous hypoglycemic episodes. A retrospective study of 47,970 diabetes patients found that patients with an A1C greater than 6.5% had an increased mortality rate. Practitioners must consider an individual patient's health, his/her risk of hypoglycemia, and his/her specific health risks when setting a target A1C level. For example, patients at high risk of microvascular complications may gain further benefits from reducing A1C below 7%. Because patients are responsible for averting or responding to their own hypoglycemic episodes, the patient's input and the doctor's assessment of the patient's self-care skills are also important.

A high HbA_{1c} represents poor glucose control. However, a 'good' HbA_{1c} in a patient with diabetes can still be riddled with a history of recent hypoglycemia, or even spikes of hyperglycemia. Regular blood glucose monitoring is still the best method for the analysis of overall vascular health with respect to blood sugar control. Often, patients with diabetes mellitus are scolded by their doctors for having an HbA_{1c} which is too low, because a lower A1C would indicate a likelihood of frequent hypoglycemia in the recent past. This is often assessed with blood sugar data, and receptions are typically mixed. A balance of long-term health (hyperglycemia prevention) versus short-term health (hypoglycemia prevention) is always a constant concern for both patients and their doctors. Doctors are especially sensitive about lower level HbA_{1c}'s with patients who regularly drive, this being a prime example of a short-term motivation for preventing hypoglycemia. Many diabetics have died behind the wheel as a result of a low blood sugar, especially for the reason that frequent hypoglycemia results in a higher tolerance (sometimes, the patient is seized with a feeling of panic, an increased heart rate, profuse sweating, etc.) for the condition, and some patients may not even consciously realize their blood sugar has dropped to dangerous levels. In addition to acquired tolerance, the use of alcohol and certain drugs (marijuana, for example) can create moderately similar symptoms to those of hypoglycemia (especially when used in combination) and for this reason the patient may not realize he/she has developed hypoglycemia.

Persistent elevations in blood sugar (and, therefore, HbA_{1c}) increase the risk for the long-term vascular complications of diabetes such as coronary disease, heart attack, stroke, heart failure, kidney failure, blindness, erectile dysfunction, neuropathy (loss of sensation, especially in the feet), gangrene, and gastroparesis (slowed emptying of the stomach). Poor blood glucose control also increases the risk of short-term complications of surgery such as poor wound healing.

Lower-than-expected levels of HbA_{1c} can be seen in people with shortened red blood cell lifespan, such as with glucose-6-phosphate dehydrogenase deficiency, sickle-cell disease, or any other condition causing premature red blood cell death. On the converse, higher-than-expected levels can be seen in people with a longer red blood cell lifespan, such as with Vitamin B_{12} or folate deficiency.

The approximate mapping between HbA_{1c} values and eAG (estimated average glucose) measurements is given by the following equation:

$$\text{eAG(mg/dl)} = 28.7 \times \text{A1C} - 46.7$$
$$\text{eAG(mmol/l)} = 1.59 \times \text{A1C} - 2.59$$

Data in parentheses are 95% confidence intervals

HbA_{1c}	**eAG (estimated average glucose)**	
(%)	**(mmol/L)**	**(mg/dL)**
5	5.4 (4.2–6.7)	97 (76–120)
6	7.0 (5.5–8.5)	126 (100–152)
7	8.6 (6.8–10.3)	154 (123–185)
8	10.2 (8.1–12.1)	183 (147–217)

9	11.8 (9.4–13.9)	212 (170–249)
10	13.4 (10.7–15.7)	240 (193–282)
11	14.9 (12.0–17.5)	269 (217–314)
12	16.5 (13.3–19.3)	298 (240–347)

Indications and use

Glycated hemoglobin testing is recommended for both (a) checking blood sugar control in people who might be pre-diabetic and (b) monitoring blood sugar control in patients with more elevated levels, termed diabetes mellitus. There is a significant proportion of people who are unaware of their elevated HbA_{1c} level before they have blood lab work. For a single blood sample, it provides far more revealing information on glycemic behavior than a fasting blood sugar value: Fasting blood sugar tests are crucial in making treatment decisions. The American Diabetes Association guidelines are similar to others in advising that the glycosylated hemoglobin test be performed at least two times a year in patients with diabetes that are meeting treatment goals (and that have stable glycemic control) and quarterly in patients with diabetes whose therapy has changed or that are not meeting glycemic goals.

Glycated hemoglobin measurement is not appropriate where there has been a change in diet or treatment within 6 weeks. Likewise, the test assumes a normal red blood cell aging process and mix of hemoglobin subtypes (predominantly HbA in normal adults). Hence, people with recent blood loss, hemolytic anemia, or genetic differences in the hemoglobin molecule (hemoglobinopathy) such as sickle-cell disease and other conditions, as well as those that have donated blood recently, are not suitable for this test.

Due to glycated hemoglobin's variability (as shown in the table above), additional measures should be checked in patients at or near recommended goals. People with hemoglobin A1C values at 8.0% or less should be provided additional testing to determine whether the HbA_{1c} values are due to averaging out high blood glucose (hyperglycemia) with low blood glucose (hypoglycemia) or the HbA_{1c} is more reflective of an elevated blood glucose that does not vary much throughout the day. Devices such as continuous blood glucose monitoring allow people with diabetes to determine their blood glucose levels on a continuous basis, testing every few minutes. Continuous use of blood glucose monitors is becoming more common, and the devices are covered by many health insurance plans but not by Medicare. The supplies tend to be expensive, since the sensors must be changed at least weekly. Another test that is useful in determining if HbA_{1c} values are due to wide variations of blood glucose throughout the day is 1,5 Anhydroglucitol, also known as GlycoMark. GlycoMark reflects only the times that the person experiences hyperglycemia above 180 mg/dL over a two-week period.

Concentrations of hemoglobin A1 (HbA1) are increased, both in diabetic patients and in patients with renal failure, when measured by ion-exchange chromatography. The thiobarbituric acid method (a chemical method specific for the detection of glycation) shows that patients with renal failure have values for glycated hemoglobin similar to

those observed in normal subjects, suggesting that the high values in these patients are a result of binding of something other than glucose to hemoglobin.

In autoimmune hemolytic anemia, concentrations of hemoglobin A1 (HbA1) is undetectable. Administration of prednisolone (PSL) will allow the HbA1 to be detected. The alternative fructosamine test may be used in these circumstances and it also reflects an average of blood glucose levels over the preceding 2 to 3 weeks.

All the major institutions like International Expert Committee Report, drawn from the International Diabetes Federation (IDF), the European Association for the Study of diabetes (EASD), and the American Diabetes Association (ADA), suggests the A1C level of 6.5% as a diagnostic level. The Committee Report further states that, when A1C testing cannot be done, the fasting and glucose tolerance tests be done.

Diagnosis of diabetes during pregnancy continues to require fasting and glucose tolerance measurements for gestational diabetes, and not the glycated hemoglobin.

Modification by exercise training

A meta-analysis of research done to identify the effect of two different kinds of training programs (combined aerobic and eccentric resistance exercise program and aerobic exercise only) on the glycosylated hemoglobin levels of individuals with T2DM found that the effect of combining resistance exercise with aerobic exercise improved the glucose control more than just the aerobics alone. The average effect of the training programs included reductions of glycosylated hemoglobin of 0.8 %, which was a result similar to that of long-term diet and drug or insulin therapy (which result in a reduction of 0.6–0.8 %).

Standardization & traceability

HbA1c is now standardized & traceable to IFCC methods HPLC-CE & HPLC-MS. A new unit (mmol/mol) is used as part of this standardization.

Glucose tolerance test

A **glucose tolerance test** is a medical test in which glucose is given and blood samples taken afterward to determine how quickly it is cleared from the blood. The test is usually used to test for diabetes, insulin resistance, and sometimes reactive hypoglycemia or rarer disorders of carbohydrate metabolism. In the most commonly performed version of the test, an *oral glucose tolerance test* (OGTT), a standard dose of glucose is ingested by mouth and blood levels are checked two hours later. Many variations of the GTT have been devised over the years for various purposes, with different standard doses of

glucose, different routes of administration, different intervals and durations of sampling, and various substances measured in addition to blood glucose.

Standard OGTT

Since the 1970s, the World Health Organization and other organizations interested in diabetes agreed on a standard dose and duration.

Preparation

The patient is instructed not to restrict carbohydrate intake in the days or weeks before the test. The test should not be done during an illness, as results may not reflect the patient's glucose metabolism when healthy. A full adult dose should not be given to a person weighing less than 43 kg (94 lb), or exaggerated glucoses may produce a false positive result. Usually the OGTT is performed in the morning as glucose tolerance can exhibit a diurnal rhythm with a significant decrease in the afternoon. The patient is instructed to fast (water is allowed) for 8–12 hours prior to the tests.

Procedure

1. A zero time (baseline) blood sample is drawn.
2. The patient is then given a measured dose (below) of glucose solution to drink within a 5 minute time frame.
3. Blood is drawn at intervals for measurement of glucose (blood sugar), and sometimes insulin levels. The intervals and number of samples vary according to the purpose of the test. For simple diabetes screening, the most important sample is the 2 hour sample and the 0 and 2 hour samples may be the only ones collected. Sometimes other laboratory continuous to collect blood up to 3 hours depending on the requesting physician

Dose of glucose and variations

- In the US, dosing is by weight, and since the late 1970s has been 1.75 grams of glucose per kilogram of body weight, to a maximum dose of 75 g. Prior to 1975 a dose of 100 g was often used.
- The WHO recommendation is for a 75g oral dose in all adults: the dose is adjusted for weight only in children. The dose should be drunk within 5 minutes.
- A variant is often used in pregnancy to screen for gestational diabetes, with a screening test of 50 grams over one hour. If elevated, this is followed with a test of 100 grams over three hours.

Substances measured and variations

If renal glycosuria (sugar excreted in the urine despite normal levels in the blood) is suspected, urine samples may also be collected for testing along with the fasting and 2 hour blood tests.

Interpretation of OGTT results

Fasting plasma glucose (measured before the OGTT begins) should be below 6.1 mmol/l (110 mg/dl). Fasting levels between 6.1 and 7.0 mmol/l (110 and 125 mg/dl) are borderline ("impaired fasting glycaemia"), and fasting levels repeatedly at or above 7.0 mmol/l (**126** mg/dl) are diagnostic of diabetes.

The **2 hour OGTT** glucose level should be below 7.8 mmol/l (140 mg/dl). Levels between this and 11.1 mmol/l (200 mg/dl) indicate "impaired glucose tolerance". Glucose levels above 11.1 mmol/l (**200** mg/dl) at 2 hours confirms a diagnosis of diabetes.

1999 WHO Diabetes criteria - Interpretation of Oral Glucose Tolerance Test

Glucose levels	**NORMAL**		**impaired fasting glycaemia (IFG)**		**impaired glucose tolerance (IGT)**		**Diabetes Mellitus (DM)**	
Venous Plasma	Fasting	2hrs	Fasting	2hrs	Fasting	2hrs	Fasting	2hrs
(mmol/l)	<6.1	<7.8	> 6.1 & <7.0	<7.8	<7.0	>7.8	>7.0	>11.1
(mg/dl)	<110	<140	>110 & <126	<140	<126	>140	>126	>200

Impaired glucose tolerance is often associated with insulin resistance and is often seen in Polycystic Ovarian Syndrome.

Variations

A standard 2 hour OGTT is sufficient to diagnose or exclude all forms of diabetes mellitus at all but the earliest stages of development. Longer tests have been used for a variety of other purposes, such as detecting reactive hypoglycemia or defining subsets of hypothalamic obesity. Insulin levels are sometimes measured to detect insulin resistance or deficiency.

The OGTT is of limited value in the diagnosis of reactive hypoglycemia, since (1) normal levels do not preclude the diagnosis, (2) abnormal levels do not prove that the patient's other symptoms are related to a demonstrated atypical OGTT, and (3) many people without symptoms of reactive hypoglycemia may have the late low glucoses that are said to be characteristic. Using a glucose tolerance in this context resembles use of a Rorschach test in that it is often used to support a diagnosis that the patient and doctor are already reaching agreement on based on other evidence, but it is inadequate by itself to confirm or refute the diagnosis (unlike its use for diabetes).

When the glucose is given intravenously it is termed an intravenous glucose tolerance test (IVGTT) or intravenous glucose challenge test (IVGCT). This has been used in the investigation of early insulin secretion abnormalities in prediabetic states.

Chapter 10

Hypertension

Hypertension

Automated arm blood pressure meter showing arterial hypertension (shown a systolic blood pressure 158 mmHg, diastolic blood pressure 99 mmHg and heart rate of 80 beats per minute).

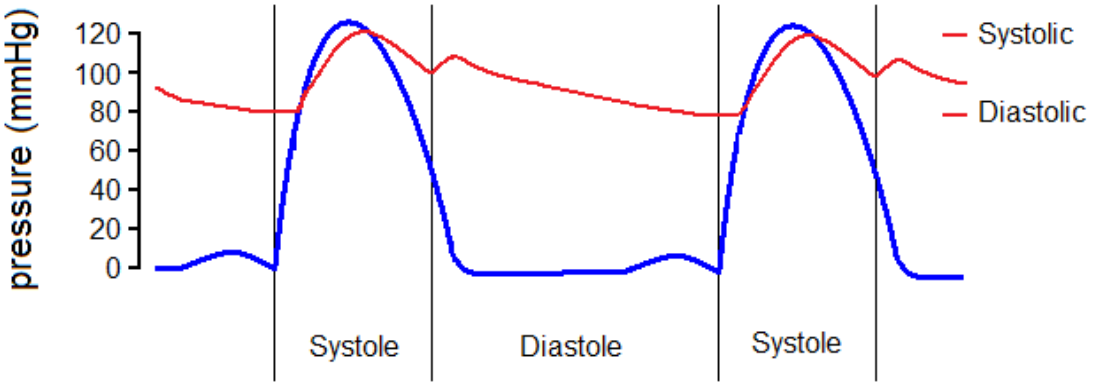
ICD-10	I10.,I11.,I12., I13.,I15.
ICD-9	401
OMIM	145500
DiseasesDB	6330
MedlinePlus	000468
eMedicine	med/1106 ped/1097 emerg/267
MeSH	D006973

Hypertension (HTN) or **high blood pressure** is a cardiac chronic medical condition in which the systemic arterial blood pressure is elevated. It is the opposite of hypotension. Hypertension is classified as either primary (essential) or secondary. About 90–95% of cases are termed "primary hypertension", which refers to high blood pressure for which no medical cause can be found. The remaining 5–10% of cases (Secondary hypertension)

are caused by other conditions that affect the kidneys, arteries, heart, or endocrine system.

Persistent hypertension is one of the risk factors for stroke, myocardial infarction, heart failure and arterial aneurysm, and is a leading cause of chronic kidney failure. Moderate elevation of arterial blood pressure leads to shortened life expectancy. Dietary and lifestyle changes can improve blood pressure control and decrease the risk of associated health complications, although drug treatment may prove necessary in patients for whom lifestyle changes prove ineffective or insufficient.

Classification



The variation in pressure in the left ventricle (blue line) and the aorta (red line) over two cardiac cycles ("heart beats"), showing the definitions of systolic and diastolic pressure

Classification	Systolic pressure		Diastolic pressure	
	mmHg	kPa	mmHg	kPa
Normal	90–119	12–15.9	60–79	8.0–10.5
Prehypertension	120–139	16.0–18.5	80–89	10.7–11.9
Stage 1	140–159	18.7–21.2	90–99	12.0–13.2
Stage 2	≥160	≥21.3	≥100	≥13.3
Isolated systolic hypertension	≥140	≥18.7	<90	<12.0

Blood pressure is usually classified based on the systolic and diastolic blood pressures. Systolic blood pressure is the blood pressure in vessels during a heart beat. Diastolic blood pressure is the pressure between heartbeats. A systolic or the diastolic blood pressure measurement higher than the accepted normal values for the age of the individual is classified as prehypertension or hypertension.

Hypertension has several sub-classifications including, hypertension stage I, hypertension stage II, and isolated systolic hypertension. Isolated systolic hypertension refers to elevated systolic pressure with normal diastolic pressure and is common in the elderly.

These classifications are made after averaging a patient's resting blood pressure readings taken on two or more office visits. Individuals older than 50 years are classified as having hypertension if their blood pressure is consistently at least 140 mmHg systolic or 90 mmHg diastolic. Patients with blood pressures higher than 130/80 mmHg with concomitant presence of diabetes mellitus or kidney disease require further treatment.

Hypertension is also classified as resistant if medications do not reduce blood pressure to normal levels.

Exercise hypertension is an excessively high elevation in blood pressure during exercise. The range considered normal for systolic values during exercise is between 200 and 230 mm Hg. Exercise hypertension may indicate that an individual is at risk for developing hypertension at rest.

Signs and symptoms

Mild to moderate essential hypertension is usually asymptomatic.

Accelerated hypertension

Accelerated hypertension is associated with headache, drowsiness, confusion, vision disorders, nausea, and vomiting symptoms which are collectively referred to as hypertensive encephalopathy. Hypertensive encephalopathy is caused by severe small blood vessel congestion and brain swelling, which is reversible if blood pressure is lowered.

Children

Some signs and symptoms are especially important in newborns and infants such as failure to thrive, seizures, irritability, lack of energy, and difficulty breathing. In children, hypertension can cause headache, fatigue, blurred vision, nosebleeds, and facial paralysis.

Even with the above clinical symptoms, the true incidence of pediatric hypertension is not known. In adults, hypertension has been defined due to the adverse effects caused by hypertension. However, in children, similar studies have not been performed thoroughly to link any adverse effects with the increase in blood pressure. Therefore, the prevalence of pediatric hypertension remains unknown due to the lack of scientific knowledge.

Secondary hypertension

Some additional signs and symptoms suggest that the hypertension is caused by disorders in hormone regulation. Hypertension combined with obesity distributed on the trunk of the body, accumulated fat on the back of the neck ('buffalo hump'), wide purple marks on the abdomen (abdominal striae), or the recent onset of diabetes suggests that an individual has a hormone disorder known as Cushing's syndrome. Hypertension caused by other hormone disorders such as hyperthyroidism, hypothyroidism, or growth

hormone excess will be accompanied by additional symptoms specific to these disorders. For example, hyperthyrodism can cause weight loss, tremors, heart rate abnormalities, reddening of the palms, and increased sweating. Signs and symptoms associated with growth hormone excess include coarsening of facial features, protrusion of the lower jaw, enlargement of the tongue, excessive hair growth, darkening of the skin color, and excessive sweating. Other hormone disorders like hyperaldosteronism may cause less specific symptoms such as numbness, excessive urination, excessive sweating, electrolyte imbalances and dehydration, and elevated blood alkalinity. and also cause of mental pressure.

Pregnancy

Hypertension in pregnant women is one symptom of pre-eclampsia. Pre-eclampsia can progress to a life-threatening condition called eclampsia, which is the development of protein in the urine, generalized swelling, and severe seizures. Other symptoms indicating that brain function is becoming impaired may precede these seizures such as nausea, vomiting, headaches, and vision loss.

In addition, the systemic vascular resistance and blood pressure decrease during pregnancy. The body must compensate by increasing cardiac output and blood volume to provide sufficient circulation in the utero-placental arterial bed.

Causes

Essential hypertension

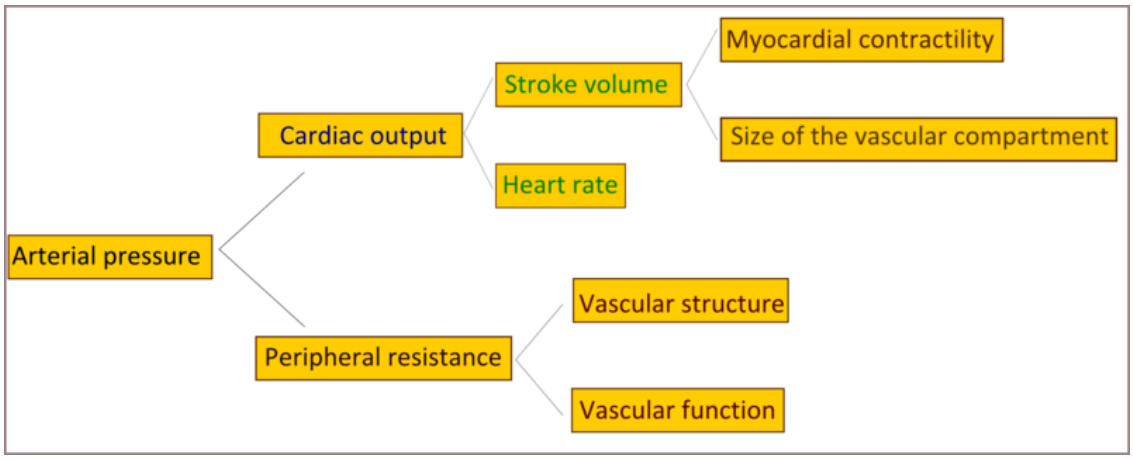
Essential hypertension is the most prevalent hypertension type, affecting 90–95% of hypertensive patients. Although no direct cause has been identified, there are many factors such as sedentary lifestyle, smoking, stress, visceral obesity, potassium deficiency (hypokalemia), obesity (more than 85% of cases occur in those with a body mass index greater than 25), salt (sodium) sensitivity, alcohol intake, and vitamin D deficiency that increase the risk of developing hypertension. Risk also increases with aging, some inherited genetic mutations, and having a family history of hypertension. An elevated level of renin, a hormone secreted by the kidney, is another risk factor, as is sympathetic nervous system overactivity. Insulin resistance, which is a component of syndrome X (or the metabolic syndrome), is also thought to contribute to hypertension. Recent studies have implicated low birth weight as a risk factor for adult essential hypertension.

Secondary hypertension

Secondary hypertension by definition results from an identifiable cause. This type is important to recognize since it's treated differently to essential hypertension, by treating the underlying cause of the elevated blood pressure. Hypertension results in the compromise or imbalance of the pathophysiological mechanisms, such as the hormone-regulating endocrine system, that regulate blood plasma volume and heart function. Many conditions cause hypertension, some are common and well recognized secondary causes

such as Cushing's syndrome, which is a condition where the adrenal glands overproduce the hormone cortisol. In addition, hypertension is caused by other conditions that cause hormone changes such as hyperthyroidism, hypothyroidism, and certain tumors of the adrenal medulla (e.g., pheochromocytoma). Other common causes of secondary hypertension include kidney disease, obesity/metabolic disorder, pre-eclampsia during pregnancy, the congenital defect known as coarctation of the aorta, and certain prescription and illegal drugs.

Pathophysiology



A diagram explaining factors affecting arterial pressure

Most of the mechanisms associated with secondary hypertension are generally fully understood. However, those associated with essential (primary) hypertension are far less understood. What is known is that cardiac output is raised early in the disease course, with total peripheral resistance (TPR) normal; over time cardiac output drops to normal levels but TPR is increased. Three theories have been proposed to explain this:

- Inability of the kidneys to excrete sodium, resulting in natriuretic factors such as Atrial Natriuretic Factor being secreted to promote salt excretion with the side effect of raising total peripheral resistance.
- An overactive Renin-angiotensin system leads to vasoconstriction and retention of sodium and water. The increase in blood volume plus vasoconstriction leads to hypertension.
- An overactive sympathetic nervous system, leading to increased stress responses.

It is also known that hypertension is highly heritable and polygenic (caused by more than one gene) and a few candidate genes have been postulated in the etiology of this condition.

Recently, work related to the association between essential hypertension and sustained endothelial damage has gained popularity among hypertension scientists. It remains unclear however whether endothelial changes precede the development of hypertension or whether such changes are mainly due to long standing elevated blood pressures.

Diagnosis

Hypertension is generally diagnosed on the basis of a persistently high blood pressure. Usually this requires three separate sphygmomanometer measurements at least one week apart. Often, this entails three separate visits to the physician's office. Initial assessment of the hypertensive patient should include a complete history and physical examination. Exceptionally, if the elevation is extreme, or if symptoms of organ damage are present then the diagnosis may be given and treatment started immediately.

Once the diagnosis of hypertension has been made, physicians will attempt to identify the underlying cause based on risk factors and other symptoms, if present. Secondary hypertension is more common in preadolescent children, with most cases caused by renal disease. Primary or essential hypertension is more common in adolescents and has multiple risk factors, including obesity and a family history of hypertension. Laboratory tests can also be performed to identify possible causes of secondary hypertension, and determine if hypertension has caused damage to the heart, eyes, and kidneys. Additional tests for Diabetes and high cholesterol levels are also usually performed because they are additional risk factors for the development of heart disease require treatment. Tests typically performed are classified as follows:

System	Tests
Renal	Microscopic urinalysis, proteinuria, serum BUN (blood urea nitrogen) and/or creatinine
Endocrine	Serum sodium, potassium, calcium, TSH (thyroid-stimulating hormone).
Metabolic	Fasting blood glucose, total cholesterol, HDL and LDL cholesterol, triglycerides
Other	Hematocrit, electrocardiogram, and chest radiograph

Creatinine (renal function) testing is done to determine if kidney disease is present, which can be either the cause or result of hypertension. In addition, it provides a baseline measurement of kidney function that can be used to monitor for side-effects of certain antihypertensive drugs on kidney function. Additionally, testing of urine samples for protein is used as a secondary indicator of kidney disease. Glucose testing is done to determine if diabetes mellitus is present. Electrocardiogram (EKG/ECG) testing is done to check for evidence of the heart being under strain from high blood pressure. It may also show if there is thickening of the heart muscle (left ventricular hypertrophy) or has experienced a prior minor heart distubance such as a silent heart attack. A chest X-ray may be performed to look for signs of heart enlargement or damage to heart tissue.

Prevention

The degree to which hypertension can be prevented depends on a number of features including current blood pressure level, sodium/potassium balance, detection and omission of environmental toxins, changes in end/target organs (retina, kidney, heart, among

others), risk factors for cardiovascular diseases and the age at diagnosis of prehypertension or at risk for hypertension. A prolonged assessment in which repeated measurements of blood pressure are taken provides the most accurate assessment of blood pressure levels. Following this, lifestyle changes are recommended to lower blood pressure, before the initiation of prescription drug therapy. The process of managing prehypertension according the guidelines of the British Hypertension Society suggest the following lifestyle changes:

- Weight reduction and regular aerobic exercise (e.g., walking): Regular exercise improves blood flow and helps to reduce the resting heart rate and blood pressure.
- Reducing dietary sugar.
- Reducing sodium (salt) in the body by disuse of condiment sodium and the adoption of a high potassium diet which rids the renal system of excess sodium. Many people use potassium chloride salt substitute to reduce their salt intake.
- Additional dietary changes beneficial to reducing blood pressure include the DASH diet (**d**ietary **a**pproaches to **s**top **h**ypertension) which is rich in fruits and vegetables and low-fat or fat-free dairy products. This diet has been shown to be effective based on research sponsored by the National Heart, Lung, and Blood Institute. In addition, an increase in dietary potassium, which offsets the effect of sodium has been shown to be highly effective in reducing blood pressure.
- Discontinuing tobacco use and alcohol consumption has been shown to lower blood pressure. The exact mechanisms are not fully understood, but blood pressure (especially systolic) always transiently increases following alcohol or nicotine consumption. Abstaining from cigarette smoking reduces the risk of stroke and heart attack which are associated with hypertension.

Limiting alcohol intake to less than 2 standard drinks per day can reduce systolic blood pressure by between 2-4mmHg.

- Reducing stress, for example with relaxation therapy, such as meditation and other mindbody relaxation techniques, by reducing environmental stress such as high sound levels and over-illumination can also lower blood pressure. Jacobson's Progressive Muscle Relaxation and biofeedback are also beneficial, such as device-guided paced breathing, although meta-analysis suggests it is not effective unless combined with other relaxation techniques.

Increasing omega 3 fatty acids can help lower hypertension. Fish oil is shown to lower blood pressure in hypertensive individuals. The fish oil may increase sodium and water excretion.

Treatment

Lifestyle modifications

The first line of treatment for hypertension is the same as the recommended preventative lifestyle changes such as the dietary changes, physical exercise, and weight loss, which

have all been shown to significantly reduce blood pressure in people with hypertension. If hypertension is high enough to justify immediate use of medications, lifestyle changes are still recommended in conjunction with medication. Drug prescription should take into account the patient's absolute cardiovascular risk (including risk of myocardial infarction and stroke) as well as blood pressure readings, in order to gain a more accurate picture of the patient's cardiovascular profile. Different programs aimed to reduce psychological stress such as biofeedback, relaxation or meditation are advertised to reduce hypertension. However, in general claims of efficacy are not supported by scientific studies, which have been in general of low quality.

Regarding dietary changes, a low sodium diet is beneficial; A Cochrane review published in 2008 concluded that a long term (more than 4 weeks) low sodium diet in Caucasians has a useful effect to reduce blood pressure, both in people with hypertension and in people with normal blood pressure. Also, the DASH diet (Dietary Approaches to Stop Hypertension) is a diet promoted by the National Heart, Lung, and Blood Institute (part of the NIH, a United States government organization) to control hypertension. A major feature of the plan is limiting intake of sodium, and it also generally encourages the consumption of nuts, whole grains, fish, poultry, fruits and vegetables while lowering the consumption of red meats, sweets, and sugar. It is also "rich in potassium, magnesium, and calcium, as well as protein".

Medications

Several classes of medications, collectively referred to as antihypertensive drugs, are currently available for treating hypertension. Agents within a particular class generally share a similar pharmacologic mechanism of action, and in many cases have an affinity for similar cellular receptors. An exception to this rule is the diuretics, which are grouped together for the sake of simplicity but actually exert their effects by a number of different mechanisms.

Reduction of the blood pressure by 5 mmHg can decrease the risk of stroke by 34%, of ischaemic heart disease by 21%, and reduce the likelihood of dementia, heart failure, and mortality from cardiovascular disease. The aim of treatment should be reduce blood pressure to <140/90 mmHg for most individuals, and lower for individuals with diabetes or kidney disease (some medical professionals recommend keeping levels below 120/80 mmHg). If the blood pressure goal is not met, a change in treatment should be made as therapeutic inertia is a clear impediment to blood pressure control. Comorbidity also plays a role in determining target blood pressure, with lower BP targets applying to patients with end-organ damage or proteinuria.

Often multiple drugs are combined to achieve the goal blood pressure. Commonly used prescription drugs include:

- ACE inhibitors (e.g., captopril)
- Alpha blockers (e.g., prazosin)
- Angiotensin II receptor antagonists (e.g., losartan)

- Beta blockers (e.g., propranolol)
- Calcium channel blockers (e.g., verapamil)
- Diuretics (e.g. hydrochlorothiazide)
- Direct renin inhibitors (e.g., aliskiren)

Some examples of common combined prescription drug treatments include:

- A fixed combination of an ACE inhibitor and a calcium channel blocker. One example of this is the combination of perindopril and amlodipine, the efficacy of which has been demonstrated in individuals with glucose intolerance or metabolic syndrome.
- A fixed combination of a diuretic and an ARB.

Combinations of an ACE inhibitor or angiotensin II–receptor antagonist, a diuretic and an NSAID (including selective COX-2 inhibitors and non-prescribed drugs such as ibuprofen) should be avoided whenever possible due to a high documented risk of acute renal failure. The combination is known colloquially as a "triple whammy" in the Australian health industry.

In the elderly

Treating moderate to severe high blood pressure with prescription medications decreases death rates in those under 80 years of age however there is no decrease in those over 80 years old. Even though there was no decrease in total mortality, the results showed similarities between cardiovascular mortality and morbidity.

Resistant

Guidelines for treating resistant hypertension have been published in the UK and US.

Complications

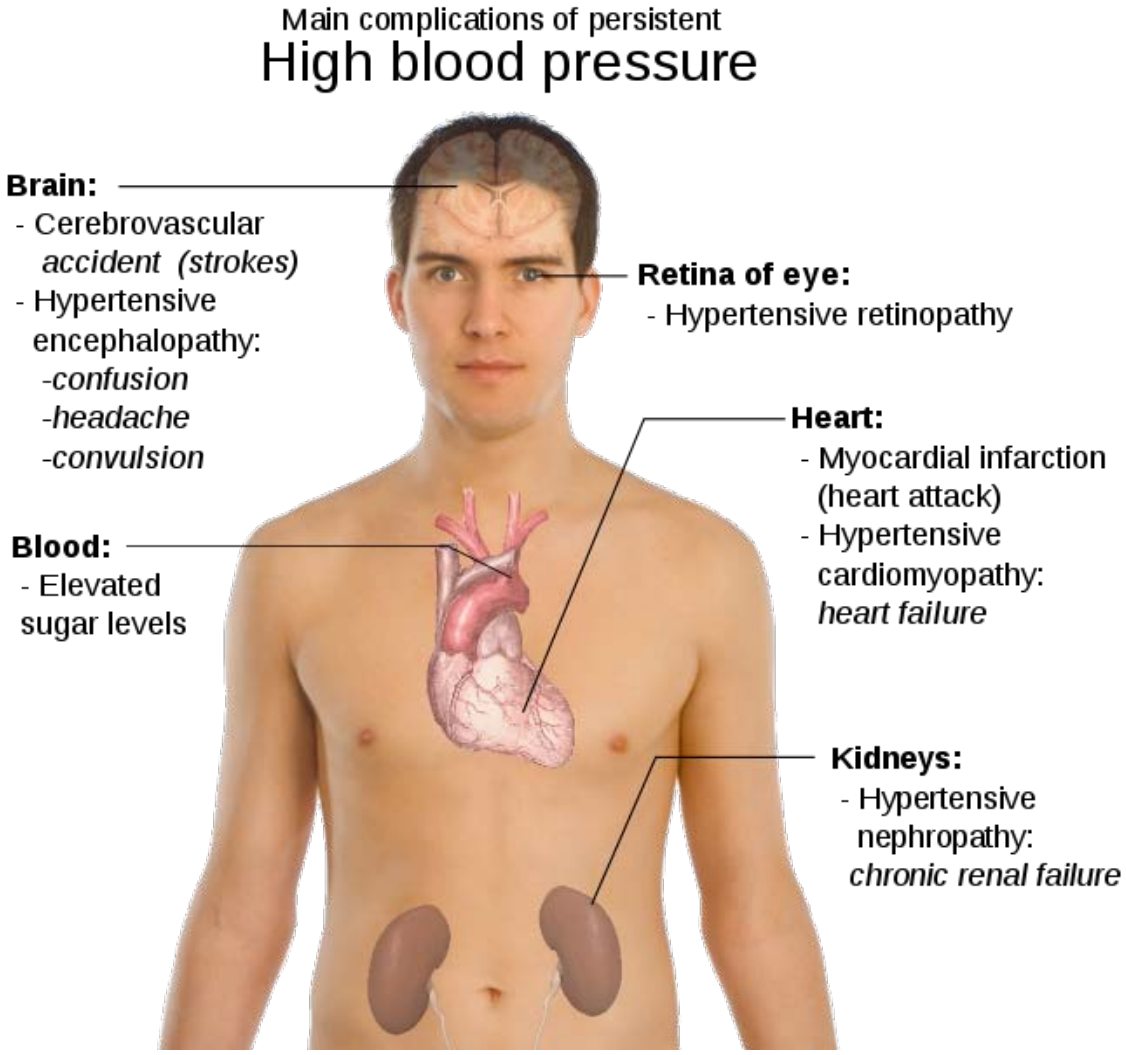


Diagram illustrating the main complications of persistent high blood pressure

Hypertension is the most important risk factor for death in industrialized countries. It increases hardening of the arteries thus predisposes individuals to heart disease, peripheral vascular disease, and strokes. Types of heart disease that may occur include: myocardial infarction, heart failure, and left ventricular hypertrophy Other complications include:

- Hypertensive retinopathy
- Hypertensive nephropathy
- If blood pressure is very high hypertensive encephalopathy may result.

Epidemiology

In the year 2000 it is estimated that nearly one billion people or ~26% of the adult population have hypertension worldwide. It was common in both developed (333 million) and undeveloped (639 million) countries. However rates vary markedly in different regions with rates as low as 3.4% (men) and 6.8% (women) in rural India and as high as 68.9% (men) and 72.5% (women) in Poland.

In 1995 it is estimated that 43 million people in the United States had hypertension or were taking antihypertensive medication, almost 24% of the adult population. The prevalence of hypertension in the United States is increasing and reached 29% in 2004. It is more common in blacks and native americans and less in whites and Mexican Americans, rates increase with age, and is greater in the southeastern United States. Hypertension is more prevalent in men (though menopause tends to decrease this difference) and those of low socioeconomic status.

Over 90–95% of adult hypertension is essential hypertension. The most common cause of secondary hypertension is primary aldosteronism. The incidence of exercise hypertension is reported to range from 1–10%.

Pediatrics

The prevalence of high blood pressure in the young is increasing. Most childhood hypertension, particularly in preadolescents, is secondary to an underlying disorder. Kidney disease is the most common (60–70%) cause of hypertension in children. Adolescents usually have primary or essential hypertension, which accounts for 85–95% of cases.

History

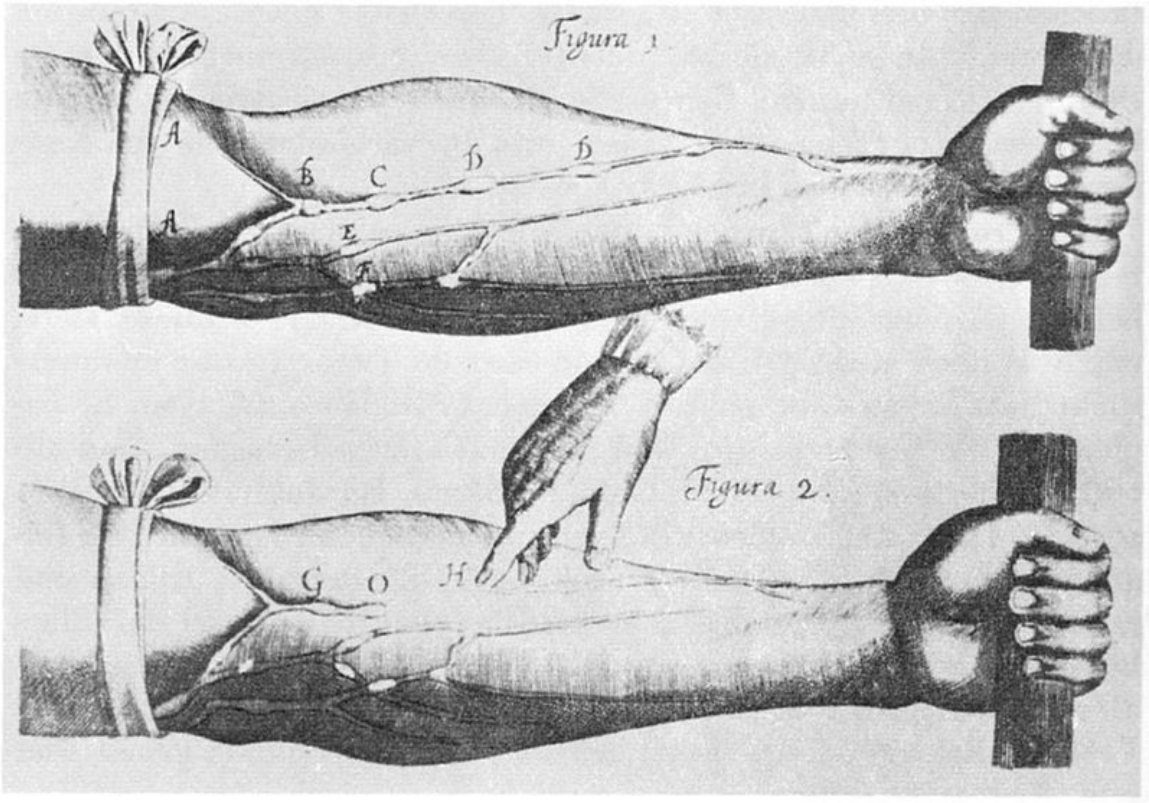


Image of veins from Harvey's *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus*

Some cite the writings of Sushruta in the 6th century BC as being the first mention of symptoms like those of hypertension. Others propose even earlier descriptions dating as far as 2600 BCE. Main treatment for what was called the "hard pulse disease" consisted in reducing the quantity of blood in a subject by the sectioning of veins or the application of leeches. Well known individuals such as The Yellow Emperor of China, Cornelius Celsus, Galen, and Hipocrates advocated such treatments.

Our modern understanding of hypertension began with the work of physician William Harvey (1578–1657), who was the first to describe correctly the systemic circulation of blood being pumped around the body by the heart in his book "*De motu cordis*". The basis for measuring blood pressure were established by Stephen Hales in 1733. Initial descriptions of hypertension as a disease came among others from Thomas Young in 1808 and specially Richard Bright in 1836. The first ever elevated blood pressure in a patient without kidney disease was reported by Frederick Mahomed (1849–1884). It was not until 1904 that sodium restriction was advocated while a rice diet was popularized around 1940.

Studies in the 1920s demonstrated the public health impact of untreated high blood pressure; treatment options were limited at the time, and deaths from malignant

hypertension and its complications were common. A prominent victim of severe hypertension leading to cerebral hemorrhage was Franklin D. Roosevelt (1882–1945). The Framingham Heart Study added to the epidemiological understanding of hypertension and its relationship with coronary artery disease. The National Institutes of Health also sponsored other population studies, which additionally showed that African Americans had a higher burden of hypertension and its complications. Before pharmacological treatment for hypertension became possible, three treatment modalities were used, all with numerous side-effects: strict sodium restriction, sympathectomy (surgical ablation of parts of the sympathetic nervous system), and pyrogen therapy (injection of substances that caused a fever, indirectly reducing blood pressure).

The first chemical for hypertension, sodium thiocyanate, was used in 1900 but had many side effects and was unpopular. Several other agents were developed after the Second World War, the most popular and reasonably effective of which were tetramethylammonium chloride and its derivative hexamethonium, hydralazine and reserpine (derived from the medicinal plant *Rauwolfia serpentina*). A randomized controlled trial sponsored by the Veterans Administration using these drugs had to be stopped early because those not receiving treatment were developing more complications and it was deemed unethical to withhold treatment from them. These studies prompted public health campaigns to increase public awareness of hypertension and the advice to get blood pressure measured and treated. These measures appear to have contributed at least in part of the observed 50% fall in stroke and ischemic heart disease beween 1972 and 1994.

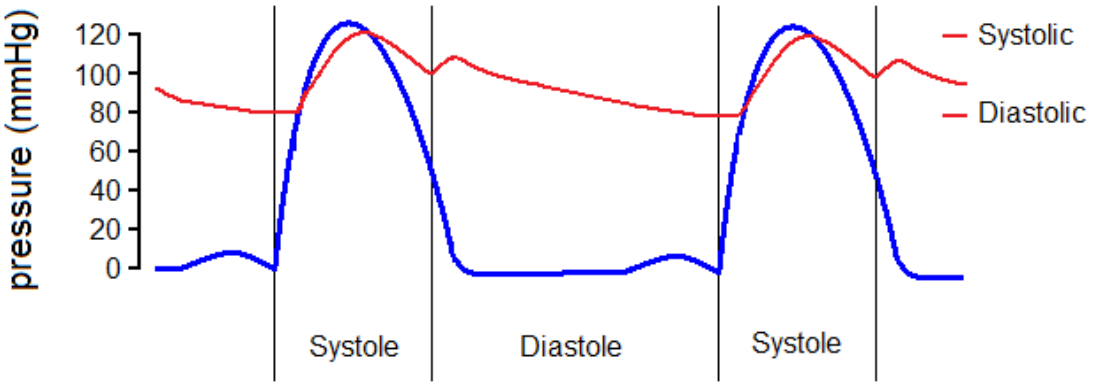
A major breakthrough was achieved with the discovery of the first well-tolerated orally available agents. The first was chlorothiazide, the first thiazide and developed from the antibiotic sulfanilamide, which became available in 1958; it increased salt excretion while preventing fluid accumulation. In 1975, the Lasker Special Public Health Award was awarded to the team that developed chlorothiazide. The British physician James W. Black developed beta blockers in the early 1960s; these were initially used for angina, but turned out to lower blood pressure. Black received the 1976 Lasker Award and in 1988 the Nobel Prize in Physiology or Medicine for his discovery. The next class of antihypertensives to be discovered was that of the calcium channel blockers. The first member was verapamil, a derivative of papaverine that was initially thought to be a beta blocker and used for angina, but then turned out to have a different mode of action and was shown to lower blood pressure. ACE inhibitors were developed through rational drug design; the renin-angiotensin system was known to play an important role in blood pressure regulation, and snake venom from *Bothrops jararaca* could lower blood pressure through inhibition of ACE. In 1977 captopril, an orally active agent, was described; this led to the development of a number of other ACE inhibitors.

Chapter 11

Essential Hypertension

Essential hypertension (also called *primary* or **idiopathic hypertension**) is the form of hypertension that by definition, has no identifiable cause. It is the most common type of hypertension, affecting 95% of hypertensive patients, it tends to be familial and is likely to be the consequence of an interaction between environmental and genetic factors. Prevalence of essential hypertension increases with age, and individuals with relatively high blood pressures at younger ages are at increased risk for the subsequent development of hypertension. It can increase risk for cerebral, cardiac, and renal events.

Classification



The variation in pressure in the left ventricle (blue line) and the aorta (red line) over two cardiac cycles ("heart beats"), showing the definitions of systolic and diastolic pressure.

A recent classification recommends blood pressure criteria for defining normal blood pressure, prehypertension, hypertension (stages I and II), and isolated systolic hypertension, which is a common occurrence among the elderly. These readings are based on the average of seated blood pressure readings that were properly measured during 2 or more office visits. In individuals older than 50 years, hypertension is considered to be present when a person's blood pressure is consistently at least 140 mmHg systolic or 90 mmHg diastolic. Patients with blood pressures over 130/80 mmHg along with Type 1 or Type 2 diabetes, or kidney disease require further treatment.

Classification	Systolic pressure		Diastolic pressure	
	mmHg	kPa (kN/m^2)	mmHg	kPa (kN/m^2)
Normal	90–119	12–15.9	60–79	8.0–10.5
Prehypertension	120–139	16.1–18.5	81–89	10.8–11.9
Stage 1	140–159	18.7–21.2	90–99	12.0–13.2
Stage 2	≥160	≥21.3	≥100	≥13.3
Isolated systolic hypertension	≥140	≥18.7	<90	<12.0

Resistant hypertension is defined as the failure to reduce blood pressure to the appropriate level after taking a three-drug regimen. Guidelines for treating resistant hypertension have been published in the UK, and US.

Risk factors

Hypertension is one of the most common complex disorders. The etiology of hypertension differs widely amongst individuals within a large population. And by definition, essential hypertension has no identifiable cause. However, several risk factors have been identified.

Hypertension may be secondary to other diseases but over 95% of patients have essential hypertension which is of unknown origin. It is observed though that:

- Having a personal family history of hypertension increases the likelihood that an individual develops HPT.
- Essential hypertension is four times more common in black than white people, accelerates more rapidly and is often more severe with higher mortality in black patients.

More than 50 genes have been examined in association studies with hypertension, and the number is constantly growing. One of these genes is the angiotensinogen (AGT) gene, studied extensively by Kim et al. They showed that increasing the number of AGT increases the blood pressure and hence this may cause hypertension. Twins have been included in studies measuring ambulatory blood pressure; from these studies it has been suggested that essential hypertension contains a large genetic influence. Supporting data has emerged from animal studies as well as clinical studies in human populations. The majority of these studies support the concept that the inheritance is probably multifactorial or that a number of different genetic defects each has an elevated blood pressure as one of its phenotypic expressions. However, the genetic influence upon hypertension is not fully understood at the moment. It is believed that linking hypertension-related phenotypes with specific variations of the genome may yield definitive evidence of heritability. Another view is that hypertension can be caused by mutations in single genes, inherited on a Mendelian basis.

Hypertension can also be age related, and if this is the case, it is likely to be multifactorial. One possible mechanism involves a reduction in vascular compliance due to the stiffening of the arteries. This can build up due to isolated systolic hypertension with a widened pulse pressure. A decrease in glomerular filtration rate is related to aging and this results in decreasing efficiency of sodium excretion. The developing of certain diseases such as renal microvascular disease and capillary rarefaction may relate to this decrease in efficiency of sodium excretion. There is experimental evidence that suggests that renal microvascular disease is an important mechanism for inducing salt-sensitive hypertension.

Obesity can increase the risk of hypertension to fivefold as compared with normal weight, and up to two-thirds of hypertension cases can be attributed to excess weight. More than 85% of cases occur in those with a Body mass index greater than 25. A definitive link between obesity and hypertension has been found using animal and clinical studies; from these it has been realized that many mechanisms are potential causes of obesity-induced hypertension. These mechanisms include the activation of the sympathetic nervous system as well as the activation of the renin–angiotensin-aldosterone system.

Another risk factor is salt (sodium) sensitivity which is an environmental factor that has received the greatest attention. Approximately one third of the essential hypertensive population is responsive to sodium intake. When sodium intake exceeds the capacity of the body to excrete it through the kidneys, vascular volume expands secondary to movement of fluids into the intra-vascular compartment. This causes the arterial pressure to rise as the cardiac output increases. Local autoregulatory mechanisms counteract this by increasing vascular resistance to maintain normotension in local vascular beds. As arterial pressure increases in response to high sodium chloride intake, urinary sodium excretion increases and the excretion of salt is maintained at expense of increased vascular pressures. The increased sodium ion concentration stimulates ADH and thirst mechanisms, leading to increased reabsorption of water in the kidneys, concentrated urine, and thirst with higher intake of water. Also, the water movement between cells and the interstitium plays a minor role compared to this. The relationship between sodium intake and blood pressure is controversial. Reducing sodium intake does reduce blood pressure, but the magnitude of the effect is insufficient to recommend a general reduction in salt intake.

Renin elevation is another risk factor. Renin is an enzyme secreted by the juxtaglomerular apparatus of the kidney and linked with aldosterone in a negative feedback loop. In consequence, some hypertensive patients have been defined as having low-renin and others as having essential hypertension. Low-renin hypertension is more common in African Americans than white Americans, and may explain why African Americans tend to respond better to diuretic therapy than drugs that interfere with the Renin-angiotensin system. High renin levels predispose to hypertension by causing sodium retention through the following mechanism: Increased renin → Increased angiotensin II → Increased vasoconstriction, thirst/ADH and aldosterone → Increased sodium reabsorption in the kidneys (DCT and CD) → Increased blood pressure.

Hypertension can also be caused by Insulin resistance and/or hyperinsulinemia, which are components of syndrome X, or the metabolic syndrome. Insulin is a polypeptide hormone secreted by cells in the islets of Langerhans, which are contained throughout the pancreas. Its main purpose is to regulate the levels of glucose in the body antagonistically with glucagon through negative feedback loops. Insulin also exhibits vasodilatory properties. In normotensive individuals, insulin may stimulate sympathetic activity without elevating mean arterial pressure. However, in more extreme conditions such as that of the metabolic syndrome, the increased sympathetic neural activity may over-ride the vasodilatory effects of insulin.

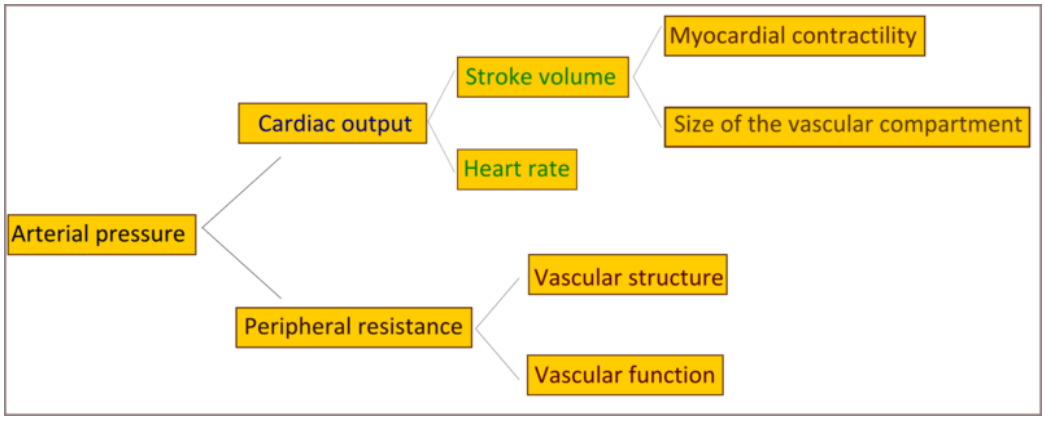
It has been suggested that vitamin D deficiency is associated with cardiovascular risk factors. It has been observed that individuals with a vitamin D deficiency have higher systolic and diastolic blood pressures than average. Vitamin D inhibits renin secretion and its activity, it therefore acts as a "negative endocrine regulator of the renin-angiotensin system". Hence a deficiency in vitamin D leads to an increase in renin secretion. This is one possible mechanism of explaining the observed link between hypertension and vitamin D levels in the blood plasma.

Also, some authorities claim that potassium might both prevent and treat hypertension.

Recent studies claims that obesity is a risk factor for hypertension because of activation of the renin-angiotensin system (RAS) in adipose tissue, and also linked renin-angiotensin system with insulin resistance, and claims that any one can cause the other.

Cigarette smoking, a known risk factor for other cardiovascular disease, may also be a risk factor for the development of hypertension.

Pathophysiology



A diagram explaining factors affecting arterial pressure

Cardiac output and peripheral resistance are the two determinants of arterial pressure. and so blood pressure is normally dependent on the balance between cardiac output and peripheral resistance. Cardiac output is determined by stroke volume and heart rate; stroke volume is related to myocardial contractility and to the size of the vascular

compartment. Peripheral resistance is determined by functional and anatomic changes in small arteries and arterioles. The pathophysiology of essential hypertension is an area of research, and until now remains not well understood, but many theories have been proposed to explain this.

What is known is that cardiac output is raised early in the disease course, with total peripheral resistance (TPR) normal; over time cardiac output drops to normal levels but TPR is increased. Three theories have been proposed to explain this:

- Inability of the kidneys to excrete sodium, resulting in natriuretic factors such as Atrial Natriuretic Factor being secreted to promote salt excretion with the side-effect of raising total peripheral resistance.
- An overactive Renin-angiotensin system leads to vasoconstriction and retention of sodium and water. The increase in blood volume leads to hypertension.
- An overactive sympathetic nervous system, leading to increased stress responses.

It is also known that hypertension is highly heritable and polygenic (caused by more than one gene) and a few candidate genes have been postulated in the etiology of this condition.

Chapter 12

Secondary Hypertension

Secondary hypertension	
ICD-10	I15.
ICD-9	405

Secondary hypertension (or, less commonly, **inessential hypertension**) is a type of hypertension which by definition is caused by an identifiable underlying secondary cause. It is much less common than the other type, called essential hypertension, affecting only 5% of hypertensive patients. It has many different causes including endocrine diseases, kidney diseases, and tumors. It also can be a side effect of many medications.

Types

Renovascular hypertension (I15.0)

It has two main causes: fibromuscular dysplasia and atheromatous stenosis.

Hypertension secondary to other renal disorders (I15.1)

- Chronic renal failure
- Kidney disease / renal artery stenosis: the normal physiological response to low blood pressure in the renal arteries is to increase cardiac output (CO) to maintain the pressure needed for glomerular filtration. Here, however, increased CO cannot solve the structural problems causing renal artery hypotension, with the result that CO remains chronically elevated.
- Renal segmental hypoplasia (Ask-Upmark kidney)

Hypertension secondary to endocrine disorders (I15.2)

- Pheochromocytoma - caused by an excessive secretion of norepinephrine and epinephrine which promotes vasoconstriction

- Hyperaldosteronism (Conn's syndrome) - idiopathic hyperaldosteronism, liddle's syndrome (also called pseudoaldosteronism), glucocorticoid remediable aldosteronism
- Cushing's syndrome - an excessive secretion of glucocorticoids causes the hypertension
- Hyperparathyroidism
- Acromegaly
- Hyperthyroidism
- Hypothyroidism

Other secondary hypertension (I15.8)

- Hormonal contraceptives
- Neurologic disorders
- Obstructive sleep apnea
- Liquorice (when consumed in excessive amounts)
- Scleroderma
- Neurofibromatosis
- Pregnancy: unclear etiology.
- Cancers: tumours in the kidney can operate in the same way as kidney disease. More commonly, however, tumors cause inessential hypertension by ectopic secretion of hormones involved in normal physiological control of blood pressure.
- Drugs: In particular, alcohol, nasal decongestants with adrenergic effects, NSAIDs, MAOIs, adrenoceptor stimulants, and combined methods of hormonal contraception (those containing ethinyl-estradiol) can cause hypertension while in use.
    - Heavy alcohol use
    - Steroid use
- Malformed aorta, slow pulse, ischemia: these cause reduced blood flow to the renal arteries, with physiological responses as already outlined.
    - Aortic valve disease: unclear etiology.
    - Coarcation of the aorta
    - Atherosclerosis
- Anemia: unclear etiology.
- Fever: unclear etiology.
- White coat hypertension, that is, elevated blood pressure in a clinical setting but not in other settings, probably due to the anxiety some people experience during a clinic visit.
- *Perioperative hypertension* is development of hypertension just before, during or after surgery. It may occur before surgery during the induction of anesthesia; intraoperatively e.g. by pain-induced sympathetic nervous system stimulation; in the early postanesthesia period, e.g. by pain-induced sympathetic stimulation, hypothermia, hypoxia, or hypervolemia from excessive intraoperative fluid therapy; and in the 24 to 48 hours after the postoperativ period as fluid is mobilized from the extravascular space. In addition, hypertension may develop

perioperatively because of discontinuation of long-term antihypertensive medication.

Adrenal

A variety of adrenal cortical abnormalities can cause hypertension, In primary aldosteronism there is a clear relationship between the aldosterone-induced sodium retention and the hypertension. Another related disorder that causes hypertension is apparent mineralocorticoid excess syndrome which is an autosomal recessive disorder that results from mutations in the gene encoding 11β-hydroxysteroid dehydrogenase, an enzyme that normally inactivates circulating cortisol to the less-active metabolite cortisone. At high concentrations cortisol can cross-react and activate the mineralocorticoid receptor, leading to aldosterone-like effects in the kidney, causing hypertension. This effect can also be produced by prolonged ingestion of liquorice (which can be of potent strength in liquorice candy), by causing inhibition of the 11β-hydroxysteroid dehydrogenase enzyme and likewise leading to secondary apparent mineralocorticoid excess syndrome. Frequently, if liquorice is the cause of the high blood pressure, a low blood level of potassium will also be present. Yet another related disorder causing hypertension is glucocorticoid remediable aldosteronism, which is an autosomal dominant disorder in which the increase in aldosterone secretion produced by ACTH is no longer transient, causing of primary hyperaldosteronism, the Gene mutated will result in an aldosterone synthase that is ACTH-sensitive, which is normally not. GRA appears to be the most common monogenic form of human hypertension. Compare these effects to those seen in Conn's disease, an adrenocortical tumor which causes excess release of aldosterone, that leads to hypertension.

Another adrenal related cause is Cushing's syndrome which is a disorder caused by high levels of cortisol. Cortisol is a hormone secreted by the cortex of the adrenal glands. Cushing's syndrome can be caused by taking glucocorticoid drugs, or by tumors that produce cortisol or adrenocorticotropic hormone (ACTH). More than 80% of patients with Cushing's syndrome develop hypertension., which is accompanied by distinct symptoms of the syndrome, such as central obesity, buffalo hump, moon face, sweating, hirsutism and anxiety.

Kidney

Other well known causes include diseases of the kidney. This includes diseases such as polycystic kidney disease which is a cystic genetic disorder of the kidneys, PKD is characterized by the presence of multiple cysts (hence, "polycystic") in both kidneys, can also damage the liver, pancreas, and rarely, the heart and brain. It can be autosomal dominant or autosomal recessive, with the autosomal dominant form being more common and characterized by progressive cyst development and bilaterally enlarged kidneys with multiple cysts, with concurrent development of hypertension, renal insufficiency and renal pain. Or chronic glomerulonephritis which is a disease characterized by inflammation of the glomeruli, or small blood vessels in the kidneys. Hypertension can also be produced by diseases of the renal arteries supplying the kidney. This is known as

renovascular hypertension; it is thought that decreased perfusion of renal tissue due to stenosis of a main or branch renal artery activates the renin-angiotensin system. also some renal tumors can cause hypertension. The differential diagnosis of a renal tumor in a young patient with hypertension includes Juxtaglomerular cell tumor, Wilms' tumor, and renal cell carcinoma, all of which may produce renin.

Neuroendocrine tumors are also a well known cause of secondary hypertension. Pheochromocytoma (most often located in the adrenal medulla) increases secretion of catecholamines such as epinephrine and norepinephrine, causing excessive stimulation of adrenergic receptors, which results in peripheral vasoconstriction and cardiac stimulation. This diagnosis is confirmed by demonstrating increased urinary excretion of epinephrine and norepinephrine and/or their metabolites (vanillylmandelic acid).

Medication side effects

Certain medications, especially NSAIDs (Motrin/Ibuprofen) and steroids can cause hypertension. High blood pressure that is associated with the sudden withdrawal of various antihypertensive medications is called rebound hypertension. The increases in blood pressure may result in blood pressures greater than when the medication was initiated. Depending on the severity of the increase in blood pressure, rebound hypertension may result in a hypertensive emergency. Rebound hypertension is avoided by gradually reducing the dose (also known as "dose tapering"), thereby giving the body enough time to adjust to reduction in dose. Medications commonly associated with rebound hypertension include centrally-acting antihypertensive agents, such as clonidine and beta-blockers.

Pregnancy

Few women of childbearing age have high blood pressure, up to 11% develop hypertension of pregnancy. While generally benign, it may herald three complications of pregnancy: pre-eclampsia, HELLP syndrome and eclampsia. Follow-up and control with medication is therefore often necessary.

Sleep disturbances

Another common and under-recognized sign of hypertension is sleep apnea, which is often best treated with nocturnal nasal continuous positive airway pressure (CPAP), but other approaches include the Mandibular advancement splint (MAS), UPPP, tonsillectomy, adenoidectomy, septoplasty, or weight loss. Another cause is an exceptionally rare neurological disease called Binswanger's disease, causing dementia; it is a rare form of multi-infarct dementia, and is one of the neurological syndromes associated with hypertension.

Arsenic exposure

Because of the ubiquity of arsenic in ground water supplies and its effect on cardiovascular health, low dose arsenic poisoning should be inferred as a part of the pathogenesis of idiopathic hypertension. Idiopathic and essential are both somewhat synonymous with primary hypertension. Arsenic exposure has also many of the same signs of primary hypertension such as headache, somnolence, confusion, proteinuria visual disturbances, and nausea and vomiting

Potassium deficiency

Due to the role of intracellular potassium in regulation of cellular pressures related to sodium, establishing potassium balance has been shown to reverse hypertension.

Diagnosis

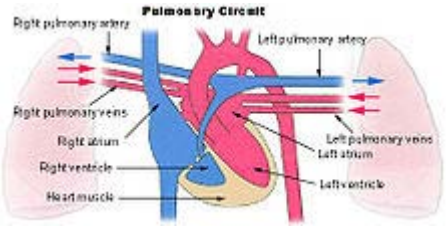
The ABCDE mnemonic can be used to help determine a secondary cause of hypertension

- A: Accuracy, Apnea, Aldosteronism
- B: Bruits, Bad Kidney
- C: Catecholamines, Coarctation of the Aorta, Cushing's Syndrome
- D: Drugs, Diet
- E: Erythropoietin, Endocrine Disorders

Chapter 13

Pulmonary Hypertension

Pulmonary arterial hypertension



Pulmonary circuit

ICD-10	I27.0, I27.2
ICD-9	416.0
DiseasesDB	10998
eMedicine	med/1962
MeSH	D006976

In medicine, **pulmonary hypertension** (PH or PAH) is an increase in blood pressure in the pulmonary artery, pulmonary vein, or pulmonary capillaries, together known as the lung vasculature, leading to shortness of breath, dizziness, fainting, and other symptoms, all of which are exacerbated by exertion. Pulmonary hypertension can be a severe disease with a markedly decreased exercise tolerance and heart failure. It was first identified by Dr. Ernst von Romberg in 1891. According to the most recent classification, it can be one of five different types: *arterial, venous, hypoxic, thromboembolic* or *miscellaneous*.

Signs and symptoms

Because symptoms may develop very gradually, patients may delay seeing a physician for years. Common symptoms are shortness of breath, fatigue, non-productive cough, angina pectoris, fainting or syncope, peripheral edema (swelling around the ankles and feet), and rarely hemoptysis (coughing up blood).

Pulmonary *venous* hypertension typically presents with shortness of breath while lying flat or sleeping (orthopnea or paroxysmal nocturnal dyspnea), while pulmonary *arterial* hypertension (PAH) typically does not.

A detailed family history is established to determine whether the disease might be familial. A history of exposure to drugs such as cocaine, methamphetamine, alcohol leading to cirrhosis, and tobacco leading to emphysema are considered significant. A physical examination is performed to look for typical signs of pulmonary hypertension, including a loud S2 (pulmonic valve closure sound), (para)sternal heave, jugular venous distension, pedal edema, ascites, hepatojugular reflux, clubbing etc. Evidence of tricuspid insufficiency is also sought and, if present, is consistent with the presence of pulmonary hypertension.

Diagnosis

Because pulmonary hypertension can be of five major types, a series of tests must be performed to distinguish pulmonary *arterial* hypertension from *venous, hypoxic, thromboembolic,* or *miscellaneous* varieties.

A physical examination is performed to look for typical signs of pulmonary hypertension. These include altered heart sounds, such as a widely split S_2 or second heart sound, a loud P_2 or pulmonic valve closure sound (part of the second heart sound), (para)sternal heave, possible S_3 or third heart sound, and pulmonary regurgitation. Other signs include an elevated jugular venous pressure, peripheral edema (swelling of the ankles and feet), ascites (abdominal swelling due to the accumulation of fluid), hepatojugular reflux, and clubbing.

Further procedures are required to confirm the presence of pulmonary hypertension and exclude other possible diagnoses. These generally include pulmonary function tests; blood tests to exclude HIV, autoimmune diseases, and liver disease; electrocardiography (ECG); arterial blood gas measurements; X-rays of the chest (followed by high-resolution CT scanning if interstitial lung disease is suspected); and ventilation-perfusion or V/Q scanning to exclude chronic thromboembolic pulmonary hypertension. Biopsy of the lung is usually not indicated unless the pulmonary hypertension is thought to be due to an underlying interstitial lung disease. But lung biopsies are fraught with risks of bleeding due to the high intrapulmonary blood pressure. Clinical improvement is often measured by a "six-minute walk test", i.e. the distance a patient can walk in six minutes. Stability and improvement in this measurement correlate with better survival. Blood BNP level is also being used now to follow progress of patients with pulmonary hypertension.

Diagnosis of PAH requires the presence of pulmonary hypertension with two other conditions. Pulmonary artery occlusion pressure (PAOP or PCWP) must be less than 15 mm Hg (2000 Pa) and pulmonary vascular resistance (PVR) must be greater than 3 Wood units (240 dyn•s•cm^{-5} or 2.4 mN•s•cm^{-5}).

Although pulmonary arterial pressure can be estimated on the basis of echocardiography, pressure measurements with a Swan-Ganz catheter provides the most definite assessment. PAOP and PVR cannot be measured directly with echocardiography. Therefore diagnosis of PAH requires right-sided cardiac catheterization. A Swan-Ganz catheter can also measure the cardiac output, which is far more important in measuring disease severity than the pulmonary arterial pressure.

Normal pulmonary arterial pressure in a person living at sea level has a mean value of 12–16 mm Hg (1600–2100 Pa). Pulmonary hypertension is present when mean pulmonary artery pressure exceeds 25 mm Hg (3300 Pa) at rest or 30 mm Hg (4000 Pa) with exercise.

Mean pulmonary artery pressure (mPAP) should not be confused with systolic pulmonary artery pressure (sPAP), which is often reported on echocardiogram reports. A systolic pressure of 40 mm Hg typically implies a *mean* pressure of more than 25 mm Hg. Roughly, mPAP = 0.61•sPAP + 2.

Causes and classification

A 1973 meeting organized by the World Health Organization was the first to attempt classification of pulmonary hypertension. A distinction was made between primary and secondary PH, and primary PH was divided in the "arterial plexiform", "veno-occlusive" and "thromboembolic" forms. A second conference in 1998 at Évian-les-Bains also addressed the causes of secondary PH (i.e. those due to other medical conditions), and in 2003, the 3rd World Symposium on Pulmonary Arterial Hypertension was convened in Venice to modify the classification based on new understandings of disease mechanisms. The revised system developed by this group provides the current framework for understanding pulmonary hypertension. The system includes several improvements over the former 1998 Evian Classification system. Risk factor descriptions were updated, and the classification of congenital systemic-to pulmonary shunts was revised. A new classification of genetic factors in PH was recommended, but not implemented because available data were judged to be inadequate.

The Venice 2003 Revised Classification system can be summarized as follows:

- WHO Group I - Pulmonary arterial hypertension (PAH)
  - Idiopathic (IPAH)
  - Familial (FPAH)
  - Associated with other diseases (APAH): collagen vascular disease (e.g. scleroderma), congenital shunts between the systemic and pulmonary circulation, portal hypertension, HIV infection, drugs, toxins, or other diseases or disorders
  - Associated with venous or capillary disease
- WHO Group II - Pulmonary hypertension associated with left heart disease
  - Atrial or ventricular disease
  - Valvular disease (e.g. mitral stenosis)

- WHO Group III - Pulmonary hypertension associated with lung diseases and/or hypoxemia
    - Chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD)
    - Sleep-disordered breathing, alveolar hypoventilation
    - Chronic exposure to high altitude
    - Developmental lung abnormalities
- WHO Group IV - Pulmonary hypertension due to chronic thrombotic and/or embolic disease
    - Pulmonary embolism in the proximal or distal pulmonary arteries
    - Embolization of other matter, such as tumor cells or parasites
- WHO Group V - Miscellaneous

The classification does not include sickle cell disease, Human herpesvirus 8, also associated with Kaposi's sarcoma, has been demonstrated in patients with PAH, suggesting that this virus may play a role in its development. Recent studies have been unable to find an association between human herpesvirus 8 and idiopathic pulmonary arterial hypertension.

Pathogenesis

Whatever the initial cause, pulmonary *arterial* hypertension (WHO Group I) involves the vasoconstriction or tightening of blood vessels connected to and within the lungs. This makes it harder for the heart to pump blood through the lungs, much as it is harder to make water flow through a narrow pipe as opposed to a wide one. Over time, the affected blood vessels become both stiffer and thicker, in a process known as fibrosis. This further increases the blood pressure within the lungs and impairs their blood flow. In addition, the increased workload of the heart causes hypertrophy of the right ventricle (a condition known as cor pulmonale), making the heart less able to pump blood through the lungs, ultimately causing right heart failure. As the blood flowing through the lungs decreases, the left side of the heart receives less blood. This blood may also carry less oxygen than normal. Therefore it becomes harder and harder for the left side of the heart to pump to supply sufficient oxygen to the rest of the body, especially during physical activity.

Pathogenesis in pulmonary *venous* hypertension (WHO Group II) is completely different. There is no obstruction to blood flow in the lungs. Instead, the left heart fails to pump blood efficiently, leading to pooling of blood in the lungs. This causes pulmonary edema and pleural effusions.

In hypoxic pulmonary hypertension (WHO Group III), the low levels of oxygen are thought to cause vasoconstriction or tightening of pulmonary arteries. This leads to a similar pathophysiology as pulmonary arterial hypertension.

In chronic thromboembolic pulmonary hypertension (WHO Group IV), the blood vessels are blocked or narrowed with blood clots. Again, this leads to a similar pathophysiology as pulmonary arterial hypertension.

Epidemiology

IPAH is a rare disease with an incidence of about 2-3 per million per year and a prevalence of about 15 per million. Adult females are almost three times as likely to present with IPAH than adult males. The presentation of IPAH within children is more evenly split along gender lines.

Other forms of PAH are far more common. In scleroderma the incidence has been estimated to be 6 to 60% of all patients, in rheumatoid arthritis up to 21%, in systemic lupus erythematosus 4 to 14%, in portal hypertension between 2 to 5%, in HIV about 0.5%, and in sickle cell disease ranging from 20 to 40%.

Diet pills such as Fen-Phen produced an annual incidence of 25-50 per million per year.

Pulmonary venous hypertension is exceedingly common, since it occurs in most patients symptomatic with congestive heart failure.

Up to 4% of people who suffer a pulmonary embolism go on to develop chronic thromboembolic disease including pulmonary hypertension.

Only about 1.1% of patients with COPD develop pulmonary hypertension with no other disease to explain the high pressure. Sleep apnea is usually associated with only very mild pulmonary hypertension, typically below the level of detection. On the other hand Pickwickian syndrome (obesity-hypoventilation syndrome) is very commonly associated with right heart failure due to pulmonary hypertension.

Treatment

Treatment is determined by whether the PH is arterial, venous, hypoxic, thromboembolic, or miscellaneous. Since pulmonary *venous* hypertension is synonymous with congestive heart failure, the treatment is to optimize left ventricular function by the use of diuretics, beta blockers, ACE inhibitors, etc., or to repair/replace the mitral valve or aortic valve.

In PAH, lifestyle changes, digoxin, diuretics, oral anticoagulants, and oxygen therapy are considered *conventional* therapy, but have never been proven to be beneficial in a randomized, prospective manner.

High dose calcium channel blockers are useful in only 5% of IPAH patients who are *vasoreactive* by Swan-Ganz catheter. Unfortunately, calcium channel blockers have been largely misused, being prescribed to many patients with non-vasoreactive PAH, leading to excess morbidity and mortality. The criteria for vasoreactivity have changed. Only those patients whose *mean* pulmonary artery pressure falls by more than 10 mm Hg to less than 40 mm Hg with an unchanged or increased cardiac output when challenged with adenosine, epoprostenol, or nitric oxide are considered vasoreactive. Of these, only half of the patients are responsive to calcium channel blockers in the long term.

A number of agents has recently been introduced for primary and secondary PAH. The trials supporting the use of these agents have been relatively small, and the only measure consistently used to compare their effectivity is the "6 minute walking test". Many have no data on mortality benefit or time to progression.

Vasoactive substances

Many pathways are involved in the abnormal proliferation and contraction of the smooth muscle cells of the pulmonary arteries in patients with pulmonary arterial hypertension. Three of these pathways are important since they have been targeted with drugs — endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, and prostacyclin derivatives.

Because inexpensive generic drugs for this disease are not widely available, the World Health Organization does not include them in its model list of essential medicines.

Prostaglandins

Prostacyclin (prostaglandin I_2) is commonly considered the most effective treatment for PAH. Epoprostenol (synthetic prostacyclin, marketed as Flolan) is given via continuous infusion that requires a semi-permanent central venous catheter. This delivery system can cause sepsis and thrombosis. Flolan is unstable, and therefore has to be kept on ice during administration. Since it has a half-life of 3 to 5 minutes, the infusion has to be continuous (24/7), and interruption can be fatal. Other prostanoids have therefore been developed. Treprostinil (Remodulin) can be given intravenously or subcutaneously, but the subcutaneous form can be very painful. An increased risk of sepsis with intravenous Remodulin has been reported by the CDC. Iloprost (Ilomedin) is also used in Europe intravenously and has a longer half life. Iloprost (marketed as Ventavis) was the only inhaled form of prostacyclin approved for use in the US and Europe, until the inhaled form of treprostinil was approved by the FDA in July 2009 and is marketed under the trade name Tyvaso. The inhaled form of administration has the advantage of selective deposition in the lungs with less systemic side effects, however coughing and throat irritation commonly occur. Oral and inhaled forms of Remodulin are under development. Beraprost is an oral prostanoid available in South Korea and Japan.

Endothelin receptor antagonists

The dual (ET_A and ET_B) endothelin receptor antagonist bosentan (marketed as Tracleer) was approved in 2001. Sitaxentan, a selective endothelin receptor antagonist that blocks only the action of ET_A, has been approved for use in Canada, Australia, and the European Union, to be marketed under the name Thelin. Sitaxentan has not been approved for marketing by the U.S. Food and Drug Administration (FDA). In 2010, Thelin was withdrawn by Pfizer due to severe side effects. A new trial to address the FDA's concerns will begin in 2008. A similar drug, ambrisentan is marketed as Letairis in U.S. by Gilead Sciences. In addition, another dual/nonselective endothelin antagonist, Actelion-1, from the makers of Tracleer, will enter clinical trials in 2008.

Phosphodiesterase type 5 inhibitors

The U.S. FDA approved Sildenafil, a selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5), for the treatment of PAH in 2005. It is marketed for PAH as Revatio. In 2009, they also approved Tadalafil, another PDE5 inhibitor, marketed under the name Adcirca.

Activators of soluble guanylate cyclase

Soluble guanylate cyclase (sGC) is the intracellular receptor for NO. As of April 2009, the sGC activators cinaciguat and riociguat are undergoing clinical trials for the treatment of PAH.

Surgical

Atrial septostomy is a surgical procedure that creates a communication between the right and left atria. It relieves pressure on the right side of the heart, but at the cost of lower oxygen levels in blood (hypoxia).

Lung transplantation cures pulmonary arterial hypertension, but leaves the patient with the complications of transplantation, and a post-surgical median survival of just over five years.

Pulmonary thromboendarterectomy (PTE) is a surgical procedure that is used for chronic thromboembolic pulmonary hypertension. It is the surgical removal of an organized thrombus (clot) along with the lining of the pulmonary artery; it is a very difficult, major procedure that is currently performed in a few select centers. Case series show remarkable success in most patients.

Treatment regimens for hypoxic and miscellaneous varieties of pulmonary hypertension have not been established. However, studies of several agents are currently enrolling patients. Many physicians will treat these diseases with the same medications as for PAH, until better options become available. Such treatment is called off-label use.

Monitoring

Patients are normally monitored through commonly available tests such as:

- pulse oximetry
- arterial blood gas tests
- chest X-rays
- serial ECG tests
- serial echocardiography
- spirometry or more advanced lung function studies

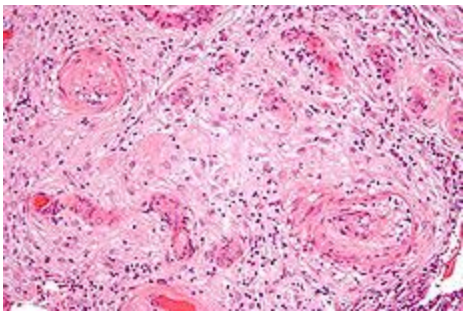
Prognosis

The NIH IPAH registry from the 1980s showed an *untreated* median survival of 2–3 years from time of diagnosis, with the cause of death usually being right ventricular failure (cor pulmonale). Although this figure is widely quoted, it is probably irrelevant today. Outcomes have changed dramatically over the last two decades. This may be because of newer drug therapy, better overall care, and earlier diagnosis (lead time bias). A recent outcome study of those patients who had started treatment with bosentan (Tracleer) showed that 89% patients were alive at 2 years. With multiple agents now available, combination therapy is increasingly used. Impact of these agents on survival is not known, since many of them have been developed only recently. It would not be unreasonable to expect median survival to extend past 10 years in the near future.

Chapter 14

Pre-eclampsia

Pre-eclampsia



Micrograph showing hypertrophic decidual vasculopathy, a histomorphologic finding seen in gestational hypertension - a component of preeclampsia. H&E stain.

ICD-10	O11., O13., O14.
ICD-9	642.4-642.7
DiseasesDB	10494
MedlinePlus	000898
eMedicine	med/1905 ped/1885
MeSH	D011225

Pre-eclampsia is a medical condition in which hypertension arises in pregnancy (pregnancy-induced hypertension) in association with significant amounts of protein in the urine.

Pre-eclampsia refers to a set of symptoms rather than any causative factor, and there are many different causes for the condition. It appears likely that there are substances from the placenta that can cause endothelial dysfunction in the maternal blood vessels of susceptible women. While blood pressure elevation is the most visible sign of the disease,

it involves generalized damage to the maternal endothelium, kidneys, and liver, with the release of vasoconstrictive factors being secondary to the original damage.

Pre-eclampsia may develop from 20 weeks gestation (it is considered early onset before 32 weeks, which is associated with increased morbidity). Its progress differs among patients; most cases are diagnosed pre-term. Pre-eclampsia may also occur up to six weeks post-partum. Apart from Caesarean section or induction of labor (and therefore delivery of the placenta), there is no known cure. It is the most common of the dangerous pregnancy complications; it may affect both the mother and the unborn child.

Diagnosis

Pre-eclampsia is diagnosed when a pregnant woman develops high blood pressure (two separate readings taken at least 6 hours apart of 140/90 or more) *and* 300 mg of protein in a 24-hour urine sample (proteinuria). A rise in baseline blood pressure (BP) of 30 mmHg systolic or 15 mmHg diastolic, while not meeting the absolute criteria of 140/90, is still considered important to note, but is not considered diagnostic. Swelling or edema (especially in the hands and face) was originally considered an important sign for a diagnosis of pre-eclampsia, but in current medical practice only hypertension and proteinuria are necessary for a diagnosis. Pitting edema (unusual swelling, particularly of the hands, feet, or face, notable by leaving an indentation when pressed on) can be significant, and should be reported to a health care provider.

"Severe preeclampsia" involves a BP over 160/110, and additional symptoms.

Pre-eclampsia may progress to eclampsia, characterized by the appearance of tonic-clonic seizures. This happens only very rarely with proper treatment.

Although eclampsia is potentially fatal, pre-eclampsia is often asymptomatic, and so its detection depends on signs or investigations. Nonetheless, one symptom is crucially important because it is often misinterpreted. The epigastric pain, which reflects hepatic involvement and is typical of the HELLP syndrome, may easily be confused with heartburn, a very common problem of pregnancy. It can be distinguished from heartburn when it is not burning in quality, does not spread upwards towards the throat, is associated with hepatic tenderness, may radiate through to the back, and is not relieved by giving antacids. It is often very severe, described by sufferers as the worst pain they have ever experienced. Affected women are not uncommonly referred to general surgeons as suffering from an acute abdomen (for example, acute cholecystitis).

In general, none of the signs of pre-eclampsia are specific, and even convulsions in pregnancy are more likely to have causes other than eclampsia in modern practice. Diagnosis, therefore, depends on finding a coincidence of several pre-eclamptic features, the final proof being their regression after delivery.

Some women develop high blood pressure without proteinuria (protein in urine), which is called pregnancy-induced hypertension (**PIH**) or gestational hypertension. Both pre-

eclampsia and PIH are regarded as very serious conditions and require careful monitoring of mother and fetus.

Epidemiology

Pre-eclampsia occurs in as many as 10% of pregnancies, usually in the second or third trimester and after the 32nd week. Some women will experience pre-eclampsia as early as 20 weeks, though this is rare. It is much more common in women who are pregnant for the first time, and its frequency drops significantly in second pregnancies. While change of paternity in a subsequent pregnancy is now thought to lower risk except in those with a family history of hypertensive pregnancy, since increasing maternal age raises risk, it has been difficult to evaluate how significant paternity change actually is and studies are providing conflicting data on this point.

Pre-eclampsia is also more common in women who have preexisting hypertension, diabetes, autoimmune diseases such as lupus, various inherited thrombophilias such as Factor V Leiden, renal disease, women with a family history of pre-eclampsia, obese women, and women with a multiple gestation (twins or multiple birth). The single most significant risk for developing pre-eclampsia is having had pre-eclampsia in a previous pregnancy.

Pre-eclampsia may also occur in the immediate post-partum period. This is referred to as "postpartum pre-eclampsia". The most dangerous time for the mother is the 24–48 hours postpartum and careful attention should be paid to pre-eclampsia signs and symptoms.

Causes

The pre-eclampsia syndrome is thought in many cases to be caused by a shallowly implanted placenta which becomes hypoxic, leading to an immune reaction characterized by secretion of upregulated inflammatory mediators from the placenta, and acting on the vascular endothelium. The shallow implantation is thought to stem from the maternal immune system's response to the placenta. This theory emphasizes the role of the maternal immune system, and refers to evidence suggesting a lack of established immunological tolerance in pregnancy, resulting in an immune response against paternal antigens from the fetus and its placenta. In some cases of pre-eclampsia it is thought that the mother lacks the receptors for the proteins the placenta is using to downregulate the maternal immune system's response to it. This view is also consistent with evidence showing many miscarriages to be an immunological disorder where the mother's immune system "unleashes a destructive attack on the tissues of the developing child."

In many cases of the pre-eclampsia syndrome, however, the maternal response to the placenta appears to have allowed for normal implantation. It is possible that women with higher baseline levels of inflammation stemming from underlying conditions such as chronic hypertension or autoimmune disease may have less tolerance for the inflammatory burden of pregnancy.

If severe, pre-eclampsia progresses to *fulminant pre-eclampsia,* with headaches, visual disturbances, and epigastric pain, and further to HELLP syndrome and eclampsia. Placental abruption is associated with hypertensive pregnancies. These are life-threatening conditions for both the developing baby and the mother.

Many theories have attempted to explain why pre-eclampsia arises, and have linked the syndrome to the presence of the following:

- endothelial cell injury
- immune rejection of the placenta
- compromised placental perfusion
- altered vascular reactivity
- imbalance between prostacyclin and thromboxane
- decreased glomerular filtration rate with retention of salt and water
- decreased intravascular volume
- increased central nervous system irritability
- disseminated intravascular coagulation
- uterine muscle stretch (ischemia)
- dietary factors, including vitamin deficiency
- genetic factors
- air pollution
- obesity

The current understanding of the syndrome is as a two-stage process, with a highly variable first stage which predisposes the placenta to hypoxia, followed by the release of soluble factors which result in many of the other observed phenomena. Many of the older theories can be subsumed under this umbrella, as the soluble factors have been shown to cause, for example, endothelial cell injury, altered vascular reactivity, the classic lesion of glomerular endotheliosis, decreased intravascular volume, inflammation, etc. Underlying maternal susceptibility to the damage is likely implicated as well.

Pathogenesis

Although much research into the etiology and mechanism of pre-eclampsia has taken place, its exact pathogenesis remains uncertain. Some studies support notions of inadequate blood supply to the placenta making it release particular hormones or chemical agents that, in mothers predisposed to the condition, leads to damage of the endothelium (lining of blood vessels), alterations in metabolism, inflammation, and other possible reactions.

Abnormalities in the maternal immune system and insufficiency of gestational immune tolerance seem to play major roles in pre-eclampsia. One of the main differences found in pre-eclampsia is a shift toward Th_1 responses and the production of IFN-γ. The origin of IFN-γ is not clearly identified and could be the natural killer cells of the uterus, the placental dendritic cells modulating responses of T helper cells, alterations in synthesis of or response to regulatory molecules, or changes in the function of regulatory T cells in

pregnancy. Aberrant immune responses promoting pre-eclampsia may also be due to an altered fetal allorecognition or to inflammatory triggers. It has been documented that fetal cells such as fetal erythroblasts as well as cell-free fetal DNA are increased in the maternal circulation in women who develop pre-eclampsia. These findings have given rise to the hypothesis that pre-eclampsia is a disease process by which a placental lesion such as hypoxia allows increased fetal material into maternal circulation that leads to an immune response and endothelial damage ultimately resulting in pre-eclampsia and eclampsia.

Some studies suggest that hypoxia resulting from inadequate perfusion upregulates sFlt-1, a VEGF and PlGF antagonist, leading to a damaged maternal endothelium and restriction of placental growth. In addition, endoglin, a TGF-beta antagonist, is elevated in pregnant women who develop pre-eclampsia. Soluble endoglin is likely upregulated by the placenta in response to an upregulation of cell-surface endoglin produced by the maternal immune system, although there is also the potential that sEng is produced by the maternal endothelium. Levels of both sFlt-1 and sEng increase as severity of disease increases, with levels of sEng surpassing levels of sFlt-1 in HELLP syndrome cases. Recent data indicate that Gadd45a stress signaling regulates elevated sFlt-1 expression in pre-eclampsia.

Both sFlt-1 and sEng are upregulated in all pregnant women to some extent, supporting the idea that hypertensive disease in pregnancy is a normal pregnancy adaptation gone awry. As natural killer cells are intimately involved in placentation and as placentation involves a degree of maternal immune tolerance for a foreign placenta which requires maternal resources for its support, it is not surprising that the maternal immune system might respond more negatively to the arrival of some placentae under certain circumstances, such as a placenta which is more invasive than normal. Initial maternal rejection of the placental cytotrophoblasts may be the cause of the inadequately remodeled spiral arteries in those cases of pre-eclampsia associated with shallow implantation, leading to downstream hypoxia and the appearance of maternal symptoms in response to upregulated sFlt-1 and sEng.

Differential diagnosis

Pre-eclampsia-eclampsia can mimic and be confused with many other diseases, including chronic hypertension, chronic renal disease, primary seizure disorders, gallbladder and pancreatic disease, immune or thrombotic thrombocytopenic purpura, antiphospholipid syndrome and hemolytic-uremic syndrome. It must always be considered a possibility in any pregnant woman beyond 20 weeks of gestation. It is particularly difficult to diagnose when preexisting disease such as hypertension is present.

Complications

Eclampsia can occur after the onset of pre-eclampsia. Eclampsia, which is a more serious condition, complicates 1 in 2000 maternities in the United Kingdom and carries a maternal mortality of 1.8 percent. The HELLP syndrome is more common, probably

about 1 in 500 maternities, but may be as dangerous as eclampsia itself. These two major maternal crises can present unheralded by prodromal signs of pre-eclampsia.

Cerebral hemorrhage is a lesion that can kill with pre-eclampsia or eclampsia. In that cerebral hemorrhage is a known complication of severe hypertension in other contexts, it must be assumed that this is a major predisposing factor in this situation, although this has not been proven. Adult respiratory distress syndrome appears to have become more common, it is not known whether this is a consequence of modern methods of respiratory support rather than of the disease itself.

Uric acid levels may help to predict maternal complications among patients with pre-eclampsia according to a systematic review and decision analysis. In this study, the sensitivity was 68% and specificity was 68%. In this study which assumed a prevalence of maternal complications was 5%, the positive predictive value of 6.2% and negative predictive value of 98.6% (click here to adjust these results for patients at higher or lower risk of maternal complications). In their clinical decision analysis, they presumed initially a distress ratio of 10 (defined as being the expected distress of severe complications valued as 10 times worse than the expected distress of a caesarean section), and under these assumptions, they concluded that there would be the least expected distress from using serum uric acid for clinical decision making. The writers of this study acknowledged that there were significant limitations to their review due to heterogeneity of the individual studies they examined with regards to several variables.

Treatment and prevention

The only known treatments for eclampsia or advancing pre-eclampsia are abortion or delivery, either by labor induction or Caesarean section. However, post-partum pre-eclampsia may occur up to 6 weeks following delivery even if symptoms were not present during the pregnancy. Post-partum pre-eclampsia is dangerous to the health of the mother since she may ignore or dismiss symptoms as simple post-delivery headaches and edema. Hypertension can sometimes be controlled with anti-hypertensive medication, but any effect this might have on the progress of the underlying disease is unknown.

Women with underlying inflammatory disorders such as chronic hypertension or autoimmune diseases would likely benefit from aggressive treatment of those conditions prior to conception, tamping down the overactive immune system.

Thrombophilias may be weakly linked to pre-eclampsia. There are no high quality studies to suggest that blood thinners will prevent pre-eclampsia in thrombophilic women.

Smoking may reduce risk of pre-eclampsia (although this association was not significant when other patient factors are taken into account) (though smoking is discouraged in pregnancy in general.)

Antihypertensive therapy

Antihypertensives may reduce maternal and fetal mortality among pregnancy patients with hypertension as compared to placebo according to a randomized controlled trial . Overall, after three weeks of treatment, MAP was lower in the isradipine group, but when compared with the placebo group, the difference in MAP did not have statistical significance. After treatment with isradipine, those patients with no proteinuria experienced a decrease of between 8.5 and 11.3 mmHg, whereas those with proteinuria experienced about only 1 mmHg difference in systolic blood pressure. Those treated with placebo in both groups did not experience much change in systolic blood pressure, regardless of proteinuria being present or not. Therefore, the authors concluded proteinuric patients may respond differently from nonproteinuric patients to this treatment, where the nonproteinuric patients responded the most to treatment with isradipine.

Labetolol or Nicardipine are also often times the antihypertensives of choice for eclampsia or pre-eclampsia according to the CHEST 2007 study. Especially Labetolol as it has little placental transfer.

Magnesium sulfate

In some cases, women with pre-eclampsia or eclampsia can be stabilized temporarily with magnesium sulfate intravenously to forestall seizures while steroid injections are administered to promote fetal lung maturation. Magnesium sulfate as a possible treatment was considered at least as far back as 1955, but only in recent years did its use in the UK replace the use of diazepam or phenytoin. Evidence for the use of magnesium sulfate came from the international MAGPIE study. When induced delivery needs to take place before 37 weeks gestation, it is accepted that there are additional risks to the baby from premature birth that will require additional monitoring and care.

Dietary and nutritional factors

Studies of protein/calorie supplementation have found no effect on pre-eclampsia rates, and dietary protein restriction does not appear to increase pre-eclampsia rates. No mechanism by which protein or calorie intake would affect either placentation or inflammation has been proposed.

Studies conducted on the effect of supplementation with antioxidants such as vitamin C and E found no change in pre-eclampsia rates. However, Drs. Padayatty and Levine with the NIH criticized the studies for overlooking several key factors that would have been important to the success of the supplementation.

Low levels of vitamin D may be a risk factor for pre-eclampsia, and calcium supplementation in women with low-calcium diets found no change in preeclampsia rates but did find a decrease in the rate of severe preeclamptic complications. Low selenium

status is associated with higher incidence of pre-eclampsia. Some other vitamin may also play a role.

Aspirin supplementation

Aspirin supplementation is still being evaluated as to dosage, timing, and population and may provide a slight preventative benefit in some women; however, significant research has been done on aspirin and the results thus far are unimpressive.

Exercise

There is insufficient evidence to recommend either exercise or bedrest as preventative measures.

Induction of paternal tolerance

Many studies have also suggested the importance of a woman's immunological tolerance to her baby's father, whose genes are present in the young fetus and its placenta and which may pose a challenge to her immune system. As the theory is further investigated, researchers are increasingly studying the importance of a woman's continued exposure to her partner's semen as early as several years before conception. One study published in the American Journal of Obstetrics and Gynecology involved several hundreds of women and found that "women with a short period of cohabitation (less than 4 months) who used barrier methods for contraception had a substantially elevated risk for the development of pre-eclampsia compared with women with more than 12 months of cohabitation before conception". However, the results from a study conducted in 2004 show that the theory is still not conclusive. In that study, the researchers found that after adjustment and stratification, the effect of barrier contraceptive use on the development of pre-eclampsia had disappeared, with both arms having identical rates of pre-eclampsia. Although the study has since then been criticized for its subjective adjustment of data, it remains important because it demonstrates that there is still some contention over the degree to which failure of tolerance induction can be attributed to prior exposure to the partner's sperm.

Continued exposure to a partner's semen has a strong protective effect against pre-eclampsia, largely due to the absorption of several immune modulating factors present in seminal fluid.

Long periods of sexual cohabitation with the same partner fathering a woman's child significantly decreased her chances of suffering pre-eclampsia. As one early study described, "although preeclampsia is a disease of first pregnancies, the protective effect of multiparity is lost with change of partner". The study also concluded that although women with changing partners are strongly advised to use condoms to prevent sexually transmitted diseases, "a certain period of sperm exposure within a stable relation, when pregnancy is aimed for, is associated with protection against preeclampsia".

Several other studies have since investigated the strongly decreased incidence of pre-eclampsia in women who had received blood transfusions from their partner, those with long, preceding histories of sex without barrier contraceptives, and in women who had been regularly performing oral sex, with one study concluding "induction of allogeneic tolerance to the paternal human leukocyte antigen (HLA) molecules of the fetus may be crucial. Data collected strongly suggest that exposure, and especially oral exposure to soluble HLA from semen can lead to transplantation tolerance."

Other studies have investigated the roles of semen in the female reproductive tracts of mice, showing that "insemination elicits inflammatory changes in female reproductive tissues", concluding that the changes "likely lead to immunological priming to paternal antigens or influence pregnancy outcomes". A similar series of studies confirmed the importance of immune modulation in female mice through the absorption of specific immune factors in semen, including TGF-Beta, lack of which is also being investigated as a cause of miscarriage in women and infertility in men.

According to the theory, the fetus and placenta both contain "foreign" proteins from paternal genes, but regular, preceding and coincident exposure to the father's semen may promote immune acceptance and subsequent implantation, a process which is significantly supported by as many as 93 currently identified immune regulating factors in seminal fluid.

Having already noted the importance of a woman's immunological tolerance to her baby's paternal genes, several Dutch reproductive biologists decided to take their research a step further. Consistent with the fact that human immune systems tolerate things better when they enter the body via the mouth, the Dutch researchers conducted a series of studies that confirmed a surprisingly strong correlation between a diminished incidence of pre-eclampsia and a woman's practice of oral sex, and noted that the protective effects were strongest if she swallowed her partner's semen. The researchers concluded that while any exposure to a partner's semen during sexual activity appears to decrease a woman's chances for the various immunological disorders that can occur during pregnancy, immunological tolerance could be most quickly established through oral introduction and gastrointestinal absorption of semen. Recognizing that some of the studies potentially included the presence of confounding factors, such as the possibility that women who regularly perform oral sex and swallow semen also engage in more frequent intercourse, the researchers also noted that, either way, "the data still overwhelmingly supports the main theory" behind all their studies—that repeated exposure to semen establishes the maternal immunological tolerance necessary for a safe and successful pregnancy.

A team from the University of Adelaide has also investigated to see if men who have fathered pregnancies which have ended in miscarriage or pre-eclampsia had low seminal levels of critical immune modulating factors such as TGF-Beta. The team has found that certain men, dubbed "dangerous males", are several times more likely to father pregnancies that would end in either pre-eclampsia or miscarriage. Among other things, most of the "dangerous males" seemed to lack sufficient levels of the seminal immune factors necessary to induce immunological tolerance in their partners.

Administration of immune factors

As the theory of immune intolerance as a cause of pre-eclampsia has become accepted, women who suffer repeated pre-eclampsia, miscarriages, or In Vitro Fertilization failures could potentially be administered key immune factors such as TGF-beta along with the father's foreign proteins, possibly either orally, as a sublingual spray, or as a vaginal gel to be applied onto the vaginal wall before intercourse.

In 2006, researchers at the University of Adelaide developed a gel containing TGF-Beta for use in human populations. Later, GroPep, the company which was awarded the patent on a TGF-Beta3 variant, conducted trials where the miscarriage rate was halved in the mice studied. According to a GroPep news release later published, "a faulty immune response is implicated in the etiology of as many as 50% of all miscarriages." Their drug, PV903, was "targeted to treat recurrent miscarriages caused by an abnormal immune response to the foetus, a condition for which there is no current [drug] treatment." Stage I clinical trials of their vaginal gel were partly successful, succeeding in establishing the safety of the drug, but failing in their aim of increasing the number of specific immune cells measured in circulation, the necessary condition for affecting a desired immunological desensitization. The trials were later criticized for failing to recognize the synergistic effects of a large variety of immune factors naturally present in seminal fluid, which, acting together and with the localized presence of the foreign paternal proteins, modulate the female immune response so as to allow for implantation, and then the subsequent immune acceptance of the (foreign) fetus throughout a successful pregnancy. GroPep was later acquired by the biotechnology giant, Novozymes. The development of the PV903 drug has since then been placed on hold.

Chapter 15

Salt and Human Physiology

Table salt

Salt consumption has been intensely studied for its role in human physiology and impact on human health. In particular, excessive dietary salt consumption over an extended period of time has been associated with hypertension and cardiovascular disease, in addition to other adverse health effects.

Most forms of edible salt are composed primarily of sodium and chloride, as other minerals such as magnesium and calcium, make unrefined salts bitter and therefore rarely eaten. An excessive intake of the ionic compound sodium chloride has long been

suspected to increase blood pressure. Sodium and chloride serum levels are both carefully controlled by the kidneys, and acute and chronic excessive intake of both ions can cause adverse health effect. However, only serum sodium is thought to be strongly correlated to blood pressure levels and cardiovascular disease.

Effect of Salt on Blood Pressure

Automated blood pressure device

The human body has evolved to balance salt intake with need through means such as the renin-angiotensin system. In humans, salt plays two important biological functions. Relevant to risk of cardiovascular disease, salt is highly involved with the maintenance of body fluid volume, including osmotic balance in the blood, extracellular and intracellular fluids.

The well known effect of sodium on blood pressure can be explained by comparing blood to a solution with its salinity changed by ingested salt. Artery walls are analogous to a selectively permeable membrane which allows sodium chloride to enter the blood stream.

Circulating water and solutes in the body maintains blood pressure in the blood, as well as other functions such as regulation of body temperature. When too much salt is ingested, it is dissolved in the blood as two separate ions - Na+ and Cl+. The water potential in blood will decrease due to the increase solutes, and blood osmotic pressure

will increase. While the kidney reacts to excrete excess sodium and chloride in the body, water retention causes blood pressure to increase inside blood vessel walls.

Blood pressure may continue to build as water is consumed hours after salt is ingested. As excess sodium is excreted by the kidneys, blood pressure drops accordingly. Diets that consistently contain high salt content will increase blood pressure over time. Fortunately, as many studies have shown, limiting salt intake in the diet can reverse these effects.

since most cases of hypertension are essential hypertension, it is unlikely that a single factor can be attributed to the cause of hypertension in most hypertensive patients.

DASH-Sodium Study

The DASH-Sodium study was a sequel to the original DASH(Dietary Approaches to Stop Hypertension study. Both studies were designed and conducted by the National Heart, Lung, and Blood Institute in the United States, each involving a large, randomized sample. While the original study was designed to test the effects of several varying nutrients on blood pressure, DASH-Sodium varies only in salt content in the diet.

Participants were pre-hypertensive or at stage 1 hypertension, and either ate a DASH-Diet or a diet reflecting an "average American Diet". During the intervention phase, participants ate their assigned diets containing three distinct levels of sodium in random order. Their blood pressure is monitored during the control period, and at all three intervention phases.

The study concluded that the effect of a reduced dietary sodium intake alone on blood pressure is substantial, and that the largest decrease in blood pressure occurred in those eating the DASH eating plan at the lowest sodium level (1,500 milligrams per day). However, this study is especially significant because participants in both the control and DASH diet group showed lowered blood pressure with decreased sodium alone.

In agreement with studies regarding salt sensitivity, participants of African descent showed high reductions in blood pressure.

Hypertension and Cardiovascular Disease

There has been strong evidence from epidemiological studies, human and animal intervention experiments, supporting the links between high rate of salt intake, hypertension and cardiovascular diseases. Short term studies have proven that a decrease in dietary salt intake will decrease blood pressure, irrespective of sex, race, age, physical activity level, and body mass. However, to properly study the effects of sodium intake levels on risk of development of cardiovascular disease, long term studies of large groups using both dietary and biochemical measures are necessary. Most of these studies, with a few exceptions, show statistical significance that groups with sodium reduced diets show lower incidences of cardiovascular disease in all demographics. A study by Cook and

colleagues were the first to show reduction of cardiovascular disease after 15 years of sodium reduction in a randomised trial.

More data is needed to support the conclusions of observational studies which suffer from design flaws. Many of these studies are not large enough, nor last long enough to provide conclusions on clinical outcomes for the effect of dietary sodium intake on morbidity and mortality. Previous mixed results and inconclusive interpretation of non-experimental studies may also root from the way sodium is measured in the study.

Current Trends and Campaigns

According to the 2004 Canadian Community Health Survey (CCHS) Canadians in all age groups are consuming sodium between 45.1 - 98.8% above the upper limit set for their gender and age group. The US Department of Agriculture claim that the average daily sodium intake for Americans over 2 years of age is 3436 mg. The majority of sodium consumed by North Americans are from processed and restaurant foods, while only a small portion is added during cooking or at the table.

Sodium Sensitivity

A diet high in sodium increase hypertension more in people with sodium sensitivity, corresponding to increase in health risks associated with hypertensions including cardiovascular disease.

Unfortunately, there is no universal definition of sodium sensitivity; as well, the method to assess sodium sensitivity varies from one study to another. In most studies, sodium sensitivity is defined as the change in mean blood pressure corresponding to a decrease or increase of sodium intake. The method to assess sodium sensitivity includes the measurement of circulating fluid volume and peripheral vascular resistance. Several studies have shown a relationship between sodium sensitivity and the increase of circulating fluid volume or peripheral vascular resistance.

A number of factors have been found to be associated with sodium sensitivity. Demographic factors which affect sodium sensitivity include race, gender, and age. One study shows that the American population of African descent are significantly more salt sensitive than those Caucasians. Women are found to be more sodium sensitive than men; one possible explanation is based on the fact that women have a tendency to consume more salt per unit weight, as women weigh less than men on average. Several studies have shown that the increase in age is also associated with the occurrence of sodium sensitivity.

The difference in genetic makeup and family history has a significant impact on salt sensitivity, and is being studied more with improvement on the efficiencies and techniques of genetic testing. In both hypertensive and non-hypertensive individuals, those with haptoglobin 1-1 phenotype are more likely to have sodium sensitivity than people with haptoglobin 2-1 or 2-2 phenotypes. More specifically, haptoglobin 2-2

phenotypes contribute to the characteristic of sodium-resistance in humans. Moreover, prevalence of a family history of hypertension is strongly linked with the occurrence of sodium sensitivity.

The influence of physiological factors including renal function and insulin leverls on sodium sensitivity are shown in various studies. One study concludes that the effect of renal failure on sodium sensitivity is substantial due to the contributtion of decreasing the Glomerular filtration rate (GFR) in the kidney. Moreover, insulin resistance is found to be related to sodium sensitivity; however, the actual mechanism is not still unknown.

Potassium and hypertension

Different salts contain different minerals contents

Possible mechanisms by which high intakes of dietary potassium can decreases risk of hypertension and instances of cardiovascular disease have been proposed but not extensively studied. However studies have found a strong inverse association between long-term adequate to high rates of potassium intake and the development of cardiovascular diseases.

The recommended dietary intake of potassium is higher than that of sodium. Unfortunately, the average absolute intake of potassium of studied populations is lower than that of sodium intake. According to Statistics Canada, Canadian's potassium intake in all age groups are lower than recommended, while sodium intake greatly exceed recommended intake in every age group.

It has been hypothesized that the ratio of potassium to sodium intake accounts for the large difference in the occurrence of hypertension between primitive cultures eating diets made up of mostly unprocessed foods and Western diets which tend to include highly processed foods.

Salt substitutes

The growing awareness of excessive sodium consumption in connection with hypertension and cardiovascular disease have increased the usage of salt substitutes at both a consumer and industrial level.

On a consumer level, salt substitutes, which usually substitutes a portion of sodium chloride content with potassium chloride, can be used to increase the potassium to sodium consumption ratio. This change has been shown to blunt the effects of excess salt intake on hypertension and cardiovascular disease. It has also been suggested that salt substitutes can be used to provide a essential portion of daily potassium intake, and may even be more economical than prescription potassium supplements.

In the food industry, processes have been developed to create low sodium versions of existing products. The meat industry especially have developed and fine tuned methods to decrease salt contents in processed meats without sacrificing consumer acceptance. Research demonstrates that salt substitutes such as potassium chloride, and synergistic compounds such as phosphates, can be used to decrease salt content in meat products.

Note that there have been concerns with certain populations' use of potassium chloride as a substitute for salt as high potassium loads are dangerous for groups with diabetes, renal diseases, heart failure. The use of salts with minerals such as natural salts have also been tested, but like salt substitutes partially containing potassium, mineral salts produce a bitter taste above certain levels.

Chapter 16

Hypertensive Emergency

A **hypertensive emergency** is severe hypertension (high blood pressure) with acute impairment of an organ system (especially the central nervous system, cardiovascular system and/or the renal system) and the possibility of irreversible organ-damage. In case of a hypertensive emergency, the blood pressure should be substantially lowered over minutes to hours with an antihypertensive agent.

Several classes of antihypertensive agents are recommended and the choice for the antihypertensive agent depends on the cause for the hypertensive crisis, the severity of elevated blood pressure and the patient's usual blood pressure before the hypertensive crisis. In most cases, the administration of an intravenous sodium nitroprusside injection which has an almost immediate antihypertensive effect is suitable but in many cases not readily available. In less urgent cases, oral agents like captopril, clonidine, labetalol, prazosin, which all have a delayed onset of action by several minutes compared to sodium nitroprusside, can also be used.

It is also important that the blood pressure is lowered not too abruptly, but smoothly. The initial goal in hypertensive emergencies is to reduce the pressure by no more than 25% (within minutes to 1 or 2 hours) and then toward a level of 160/100 mm Hg within 2–6 hours. Excessive reductions in pressure may precipitate coronary, cerebral, or renal ischemia. The diagnosis of a hypertensive emergency is not only based on the absolute level of blood pressure, but also on the individual regular level of blood pressure before the hypertensive crisis. Individuals with a history of chronic hypertension may not tolerate a "normal" blood pressure.

Incidence

Hypertensive crisis affects upward of 500,000 Americans each year. Although the incidence of hypertensive crisis is low, affecting fewer than 1% of hypertensive adults, more than 50 million adult Americans suffer from hypertension.

According to a research published in 2006, hypertension prevalence is again on the rise with 28.6% of the U.S. population suffering it in 1999-2002. According to the study, incidence rates of hypertension range between 3% and 18%. These numbers depend on the age, gender, ethnicity, and body size.

According to Whelton, the incidence and prevalence of hypertension is about 50% higher in African-American adults than in white or Mexican-American populations. Also, Whelton adds that prevalence of hypertension has increased progressively in children and adolescents between 1988-2000. According to the study recent estimates indicate that approximately 1 billion adults have hypertension. The highest prevalence of hypertension is in Eastern Europe and the Latin American/Caribbean region.

As a result of the use of antihypertensives, the incidence of hypertensive emergencies has declined from 7% to 1% of patients with hypertension. The 1 – year survival rate has also increased. Before 1950, this survival rate was only 20%, and it is now more than 90% with the proper medical treatment. Hypertensive crises affect less than 1% of hypertensive adults in the United States.

Hypertensive crises more commonly occur among blacks and the elderly. Most patients who experience hypertensive crises have previously been diagnosed as hypertensive. Many of such patients have been prescribed antihypertensive therapy , but have inadequate blood pressure control.

Estimates indicate that approximately 1% to 2% of patients with hypertension develop hypertensive crisis at some point in their lifetime. Men are usually more affected by hypertensive crises than women.

The incidence of hypertensive crises has increased and hospital admissions tripled between 1983 and 1990, from 23,000 to 73,000 per year in the United States. The incidence of postoperative hypertensive crisis varies and such variation depends on the population examined. Most studies report and incidence of between 4% to 35%.

Terminology

Generally, the terminology describing hypertensive emergencies can be confusing. Terms such as **hypertensive crisis**, malignant hypertension, **hypertensive urgency**, accelerated hypertension and severe hypertension are all used in the literature and often overlap.

Hypertensive emergency as a specific term

The term hypertensive emergency is primarily used as a specific term for a hypertensive crisis with a diastolic blood pressure of 120 mm Hg and above plus end organ damage (brain, cardiovascular, renal) (as described above) in contrast to hypertensive urgency where as yet no end organ damage has developed. The former requires immediate lowering of blood pressure such as with sodium nitroprusside infusions (NOT injections) while urgencies (about 3/4 of cases with diastolic blood pressure of 120 mm Hg and above) can be treated with oral agents, with the goal of lowering the mean arterial pressure (MAP) by 20% in 1-2 days with further reduction to "normal" levels in weeks or months. The former use of oral nifedipine, a calcium channel blocker, has been strongly banned because it is not absorbed in a controlled and reproducible fashion and has led to serious and fatal hypotensive problems.

Hypertensive emergency as a generic term

Sometimes, although not very often, the term hypertensive emergency is also used as a generic term, comprising both hypertensive emergency as a specific term for a serious and urgent condition of elevated blood pressure and hypertensive urgency as a specific term of a less serious and less urgent condition (the terminology hypertensive crisis is usually used in this sense).

Pathophysiology

The pathophysiology of hypertensive emergencies is not well understood. Failure of normal autoregulation and an abrupt rise in systemic vascular resistance are typically initial steps in the disease process.

Hypertensive emergency pathophysiology includes:

- Abrupt increases in systemic vascular resistance likely related to humoral. vasoconstrictors
- Endothelial injury
- Fibrinoid necrosis of the arterioles
- Deposition of platelets and fibrin
- Breakdown of the normal autoregulatory function.
- The resulting ischemia prompts further release of vasoactive substances completing a vicious cycle.

If the process is not stopped, a vicious cycle of homeostatic failure begins, leading to loss of cerebral and local autoregulation, organ system ischemia and dysfunction and myocardial infarction.

It is estimated that in up to 83% of hypertensive emergency patients a single-organ involvement is found and two-organ involvement in nearly 14% of patients. Almost 3% of the patients are found with multi-organ failure which means failure of at least 3 organ systems.

The most common clinical presentations of hypertensive emergencies are cerebral infarction (24.5%), pulmonary edema (22.5%), hypertensive encephalopathy (16.3%), and congestive heart failure (12%). Less common presentations include. intracranial hemorrhage, aortic dissection, and eclampsia

Cerebral autoregulation is the ability of the blood vessels in the brain to maintain a constant blood flow. It has been shown that people who suffer from chronic hypertension can tolerate higher arterial pressure before their autoregulation system is disrupted and that they have an increased cerebrovascular resistance which makes them more at risk of developing cerebral ischemia if the blood flow decreases into normotensive ranges. On the other hand, sudden or rapid rises in blood pressure may cause hyperperfusion and increased cerebral blood flow, causing increased intracranial pressure and cerebral

edema. Hypertensive encephalopathy is one of the clinical manifestations of cerebral edema and microhemorrhages seen with dysfunction of cerebral autoregulation and is characterized by hypertension, altered mentation, and papilledema.

In what concerns heart damage, this seems to be caused by an increased arterial stiffness, increased systolic blood pressure, and widened pulse pressures, all of these as results of chronic hypertension. The coronary perfusion pressures are decreased by these factors, which increase the myocardial oxygen consumption as well, leading to left ventricular hypertrophy. As the left ventricle is unable to compensate for an acute rise in systemic vascular resistance, left ventricular failure and pulmonary edema or myocardial ischemia may occur.

Chronic hypertension has a great impact on the renal vasculature as well as it may cause pathologic changes to the small arteries of the kidney. The arteries develop endothelial dysfunction and impaired vasodilation, which alter renal autoregulation. When the renal autoregulatory system is disrupted, the intraglomerular pressure starts to vary directly with the systemic arterial pressure, thus offering no protection to the kidney during blood pressure fluctuations. During a hypertensive crisis, this can lead to acute renal ischemia.

Endothelial injury occurs due to severe elevations of blood pressure and fibrinoid necrosis of the arterioles follow. The vascular injury leads to deposition of platelets and fibrin, and a breakdown of the normal autoregulatory function. Ischemia occurs as a result which prompts further release of vasoactive substances. This process completes the vicious cycle.

Many factors and causes contribute in hypertension crises. One main cause is the discontinuation of antihypertensive medications. Other common causes of hypertensive crises are autonomic hyperactivity, collagen-vascular diseases, drug use including cocaine and amphetamines, glomerulonephritis, head trauma, neoplasias, preeclampsia and eclampsia, renovascular hypertension.

During a hypertensive emergency uncontrolled BPs lead to progressive or impending end-organ dysfunction; therefore, it is important to lower the BP aggressively. Acute end-organ damage may occur including neurological, cardiovascular and other. Some examples of neurological damage include hypertensive encephalopathy, cerebral vascular accident/cerebral infarction, subarachnoid hemorrhage, and intracranial hemorrhage. Cardiovascular damages include myocardial ischemia/infarction, acute left ventricular dysfunction, acute pulmonary edema, and aortic dissection. Other end-organ damage include acute renal failure or insufficiency, retinopathy, eclampsia, and microangiopathic hemolytic anemia. Also, severe blood pressure leads to problems in the eye such as retinopathy or damage to the blood vessels in the eye.

Mortality

Severe hypertension is a serious medical condition with a general poor prognosis as it is estimated that people who do not receive appropriate treatment live up to three years after the diagnosis has been established.

The morbidity and mortality of hypertensive emergencies depend on the extent of end-organ dysfunction on presentation and the degree to which blood pressure is controlled subsequently. With blood pressure control and medication compliance, the 10-year survival rate of patients with hypertensive crises approaches 70%.

The risks of developing a life-threatening disease affecting the heart or brain increase as the blood flow increase. Commonly, ischemic heart attack and stroke are the causes that lead to death in patients with severe hypertension. It is estimated that for every 20 mm Hg systolic or 10 mm Hg diastolic increase in blood pressures above 115/75 mm Hg, the mortality rate for both ischemic heart disease and stroke doubles.

Several studies have concluded that African Americans have a greater incidence of hypertension and a greater morbidity and mortality from hypertensive disease than non-Hispanic whites. It appears that hypertensive crisis is also more common in African Americans compared with other races.

Although severe hypertension is more common in the elderly, it may occur in children though very rarely. Also, women have slightly increased risks of developing hypertension crisis. The lifetime risk for hypertension is 86-90% in females and 81-83% in men.

Clinical history

The clinical history is focused on whether the end-organ dysfunction is present or not, the circumstances in which hypertension developed, and any other identifiable etiology. The clinical history is helpful in determining the type, severity, and treatment or management of the hypertensive event.

Both the history and physical examination determine the nature, severity, and management of the hypertensive event.

A complete clinical history should include detailed information on the type of medication that the patient takes. Commonly, details of antihypertensive drug therapy and compliance, intake of over-the-counter medication such as sympathomimetic agents and use of illicit drugs such as cocaine will be included in a complete clinical history.

The health care provider will need to know if the patient is taking any herbal or dietary supplements.

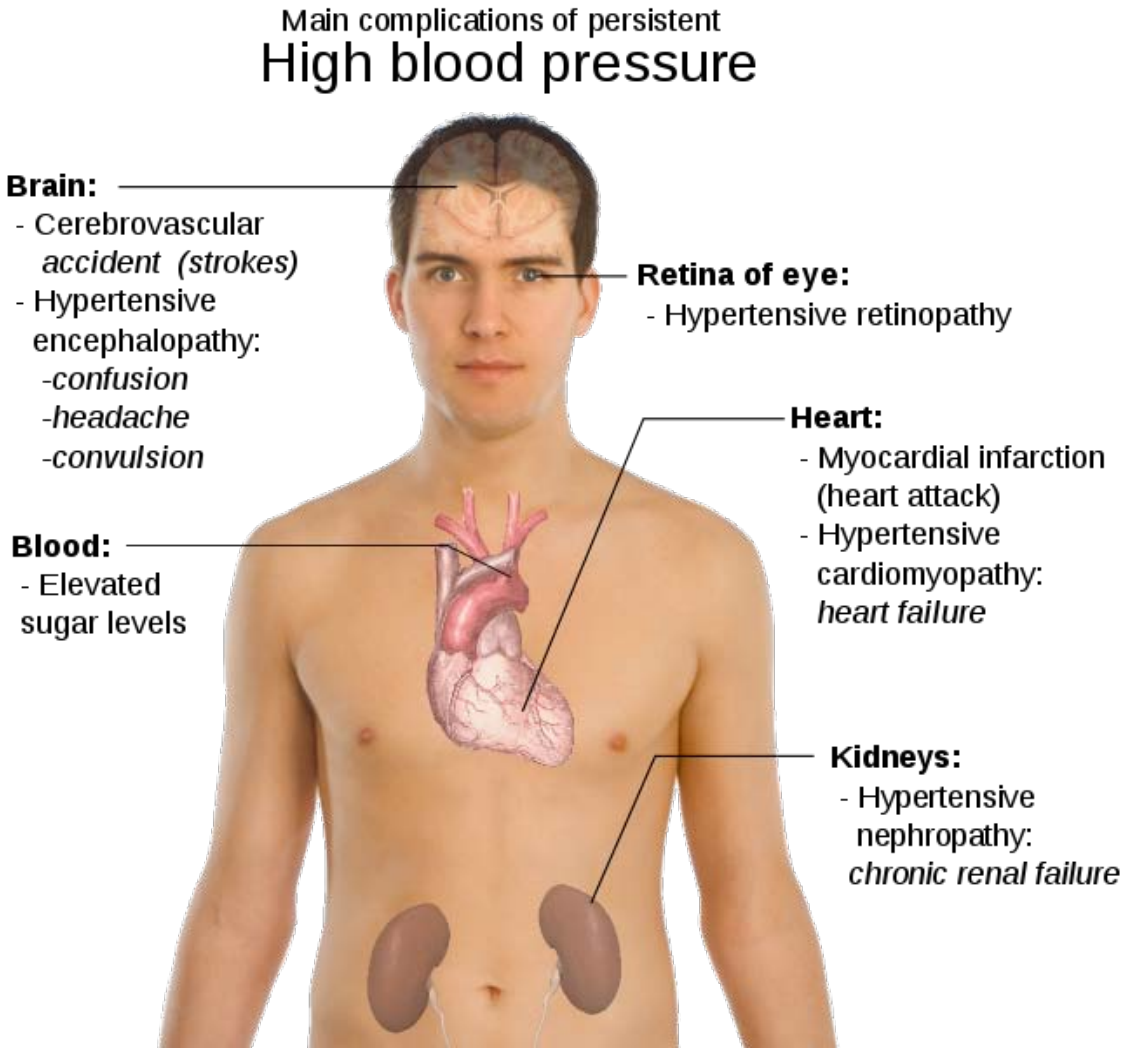
The duration and severity of preexisting hypertension, degree of blood pressure control, presence of previous end-organ dysfunction, particularly renal and cerebrovascular

disease, and date of last menstrual period or other medical conditions such as prior hypertension, thyroid disease, Cushing disease or renal disease are other factors that are considered as part of a complete medical history in suspected of severe hypertension.

Another important part of the clinical history is to determine whether specific symptoms suggesting EOD are present such as chest pain, which indicates myocardial ischemia or infarction; back pain, which indicates aortic dissection; dyspnea, as indicator of pulmonary edema and congestive heart failure; and neurologic symptoms with indicators such as seizures, visual disturbances, altered level of consciousness.

Chapter 17

Antihypertensive Drug



Antihypertensive therapy seeks to prevent the complications of high blood pressure, such as stroke and myocardial infarction.

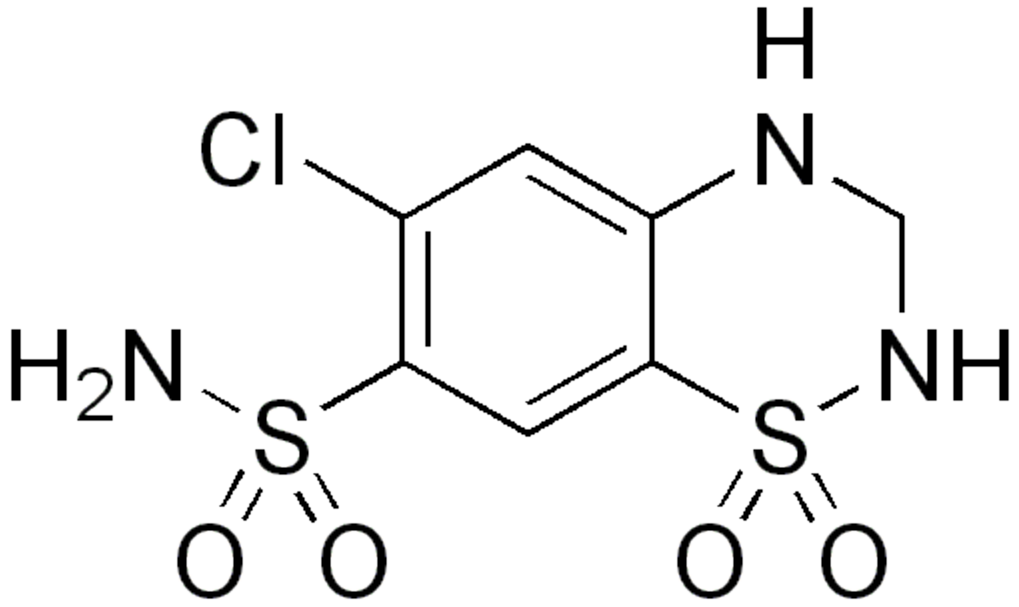
The **antihypertensives** are a class of drugs that are used to treat hypertension (high blood pressure). Evidence suggests that reduction of the blood pressure by 5 mmHg can

decrease the risk of stroke by 34%, of ischaemic heart disease by 21%, and reduce the likelihood of dementia, heart failure, and mortality from cardiovascular disease. There are many classes of antihypertensives, which lower blood pressure by different means; among the most important and most widely used are the thiazide diuretics, the ACE inhibitors, the calcium channel blockers, the beta blockers, and the angiotensin II receptor antagonists or ARBs.

Which type of medication to use initially for hypertension has been the subject of several large studies and resulting national guidelines. The fundamental goal of treatment should be the prevention of the important endpoints of hypertension, such as heart attack, stroke and heart failure. Patient age, associated clinical conditions and end-organ damage also play a part in determining dosage and type of medication administered.. The several classes of antihypertensives differ in side effect profiles, ability to prevent endpoints, and cost. The choice of more expensive agents, where cheaper ones would be equally effective, may have negative impacts on national healthcare budgets. As of 2009, the best available evidence favors the thiazide diuretics as the first-line treatment of choice for high blood pressure when drugs are necessary.

Available agents

Diuretics



Hydrochlorothiazide, a popular thiazide diuretic

Diuretics help the kidneys eliminate excess salt and water from the body's tissues and blood.

- Loop diuretics:
  - bumetanide
  - ethacrynic acid

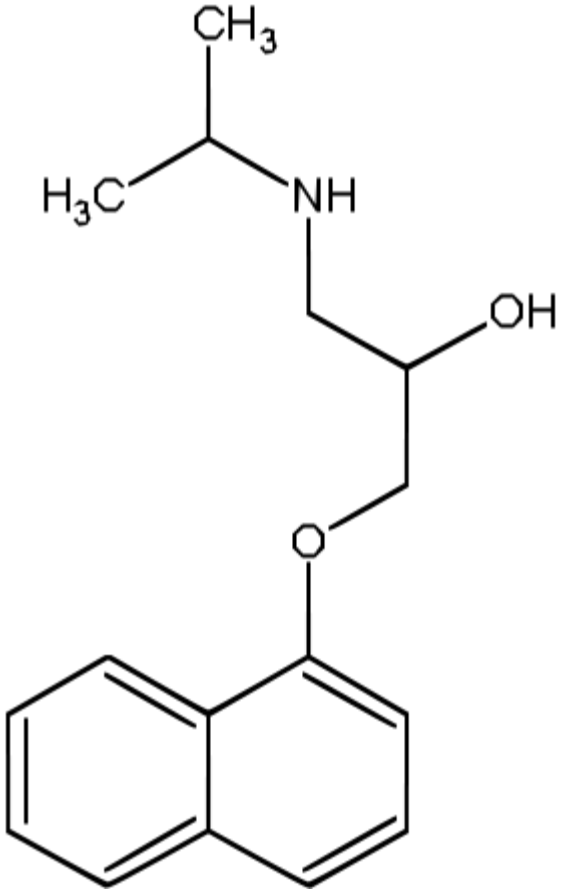
    - furosemide
    - torsemide
- Thiazide diuretics:
    - epitizide
    - hydrochlorothiazide and chlorothiazide
    - bendroflumethiazide
- Thiazide-like diuretics:
    - indapamide
    - chlorthalidone
    - metolazone
- Potassium-sparing diuretics:
    - amiloride
    - triamterene
    - spironolactone

Only the thiazide and thiazide-like diuretics have good evidence of beneficial effects on important endpoints of hypertension, and hence, should usually be the first choice when selecting a diuretic to treat hypertension. The reason why thiazide-type diuretics are better than the others is (at least in part) thought to be because of their vasodilating properties. Although the diuretic effect of thiazides may be apparent shortly after administration, it takes longer (weeks of treatment) for the full anti-hypertensive effect to develop. In the United States, the JNC7 (The Seventh Report of the Joint National Committee on Prevention of Detection, Evaluation and Treatment of High Blood Pressure) recommends starting with a thiazide diuretic if single therapy is being initiated and another medication is not indicated. This is based on a slightly better outcome for chlortalidone in the ALLHAT study versus other anti-hypertensives and because thiazide diuretics are relatively cheap. A subsequent smaller study (ANBP2) published after the JNC7 did not show this small difference in outcome and actually showed a slightly better outcome for ACE-inhibitors in older male patients.

Despite thiazides being cheap, effective, and recommended as the best first-line drug for hypertension by many experts, they are not prescribed as often as some newer drugs. This is because they have been associated with increased risk of new-onset diabetes and as such are recommended for use in patients over 65 where the risk of new-onset diabetes is outweighed by the benefits of controlling systolic blood pressure

Another theory is that they are off-patent and thus rarely promoted by the drug industry.

Adrenergic receptor antagonists



Propranolol, the first beta-blocker to be successfully developed

- Beta blockers
  - atenolol
  - metoprolol
  - nadolol
  - oxprenolol
  - pindolol
  - propranolol
  - timolol
- Alpha blockers:
  - doxazosin
  - phentolamine
  - indoramin
  - phenoxybenzamine
  - prazosin
  - terazosin
  - tolazoline
- Mixed Alpha + Beta blockers:
  - bucindolol

    - carvedilol
    - labetalol

Although beta blockers lower blood pressure, they do not have a positive benefit on endpoints as some other antihypertensives. In particular, beta-blockers are no longer recommended as first-line treatment due to relative adverse risk of stroke and new-onset diabetes when compared to other medications, while certain specific beta-blockers such as atenolol appear to be less useful in overall treatment of hypertension than several other agents. They do, however, have an important role in the prevention of heart attacks in people who have already had a heart attack. In the United Kingdom, the June 2006 "Hypertension: Management of Hypertension in Adults in Primary Care" guideline of the National Institute for Health and Clinical Excellence, downgraded the role of beta-blockers due to their risk of provoking type 2 diabetes.

Despite lowering blood pressure, alpha blockers have significantly poorer endpoint outcomes than other antihypertensives, and are no longer recommended as a first-line choice in the treatment of hypertension. However, they may be useful for some men with symptoms of prostate disease.

Adrenergic receptor agonists

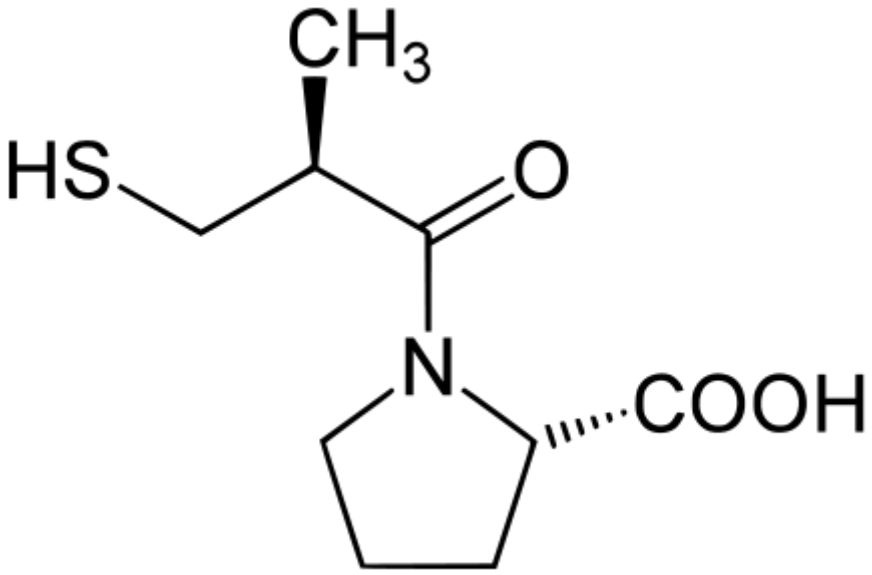
- Alpha-2 agonists:
    - clonidine
    - methyldopa
    - Guanfacine

Calcium channel blockers

Calcium channel blockers block the entry of calcium into muscle cells in artery walls.

- dihydropyridines:
    - amlodipine
    - felodipine
    - isradipine
    - lercanidipine
    - nicardipine
    - nifedipine
    - nimodipine
    - nitrendipine
- non-dihydropyridines:
    - diltiazem
    - verapamil

ACE inhibitors

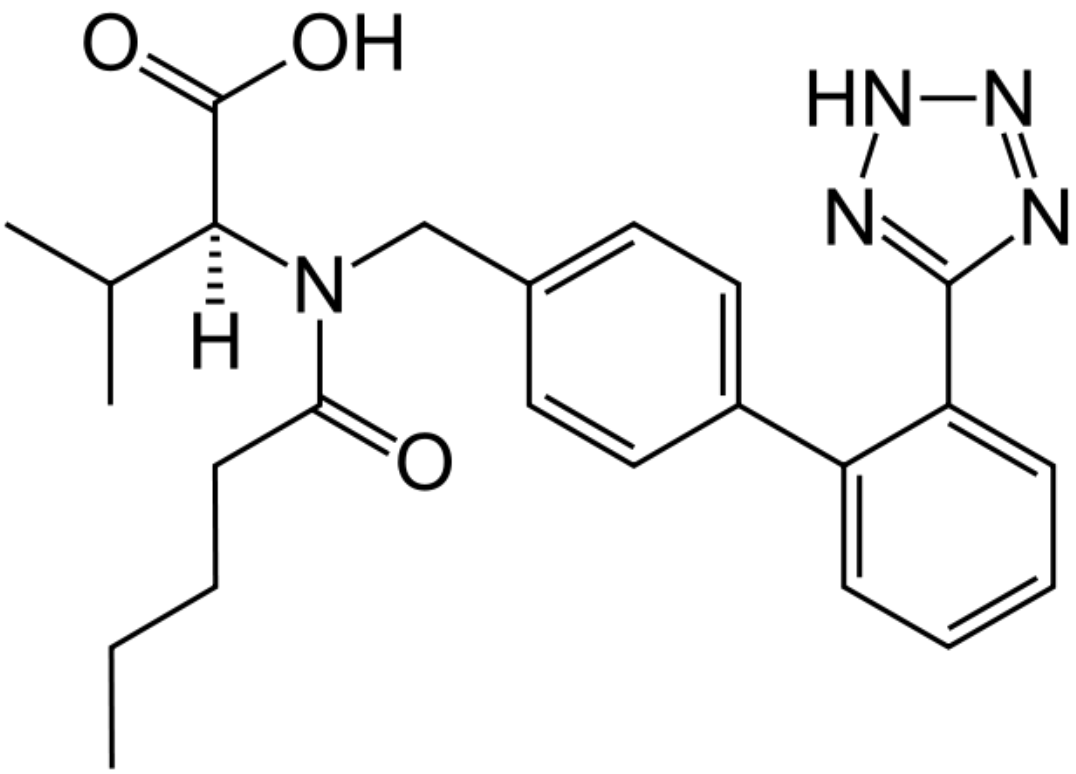


Captopril, the prototypical ACE inhibitor

ACE inhibitors inhibit the activity of Angiotensin-converting enzyme (ACE), an enzyme responsible for the conversion of angiotensin I into angiotensin II, a potent vasoconstrictor.

- captopril
- enalapril
- fosinopril
- lisinopril
- perindopril
- quinapril
- ramipril
- trandolapril
- benazepril

Angiotensin II receptor antagonists



Valsartan, an angiotensin II receptor antagonist

Angiotensin II receptor antagonists work by antagonizing the activation of angiotensin receptors.

- candesartan
- eprosartan
- irbesartan
- losartan
- olmesartan
- telmisartan
- valsartan

Aldosterone antagonists

Aldosterone receptor antagonists:

- eplerenone
- spironolactone

Aldosterone antagonists are not recommended as first-line agents for blood pressure, but spironolactone and eplerenone are both used in the treatment of heart failure.

Vasodilators

Vasodilators act directly on the smooth muscle of arteries to relax their walls so blood can move more easily through them; they are only used in hypertensive emergencies or when other drugs have failed, and even so are rarely given alone.

Sodium nitroprusside, a very potent, short-acting vasodilator, is most commonly used for the quick, temporary reduction of blood pressure in emergencies (such as malignant hypertension or aortic dissection). Hydralazine and its derivatives are also used in the treatment of severe hypertension, although they should be avoided in emergencies. They are no longer indicated as first-line therapy for high blood pressure due to side effects and safety concerns, but hydralazine remains a drug of choice in gestational hypertension.

Centrally acting adrenergic drugs

Central alpha agonists lower blood pressure by stimulating alpha-receptors in the brain which open peripheral arteries easing blood flow. Central alpha agonists, such as clonidine, are usually prescribed when all other anti-hypertensive medications have failed. For treating hypertension, these drugs are usually administered in combination with a diuretic.

- Clonidine
- Guanabenz
- Methyldopa
- Moxonidine

Adverse effects of this class of drugs include sedation, drying of the nasal mucosa and rebound hypertension.

Some adrenergic neuron blockers are used for the most resistant forms of hypertension:

- Guanethidine
- Reserpine

Future treatment options

Blood pressure vaccine

Blood pressure vaccinations are being trialed and may become a treatment option for high blood pressure in the future. Research on the vaccine CYT006-AngQb published in The Lancet on the 8 March 2008 titled, “Vaccination against high blood pressure: a new strategy” showed patients experienced a drop in systolic and diastolic blood pressure after taking the vaccine. Effective blood pressure vaccines would assist those people who forget to take their medication. It would also help those who stop taking their medication due to side effects or falsely believing they don't need them anymore once their blood pressure is lowered.

Choice of initial medication

For mild blood pressure elevation, consensus guidelines call for medically-supervised lifestyle changes and observation before recommending initiation of drug therapy. However, according to the American Hypertension Association, evidence of sustained damage to the body may be present even prior to observed elevation of blood pressure. Therefore the use of hypertensive medications may be started in individuals with apparent normal blood pressures but who show evidence of hypertension related nephropathy, proteinuria, atherosclerotic vascular disease, as well as other evidence of hypertension related organ damage.

If lifestyle changes are ineffective, then drug therapy is initiated, often requiring more than one agent to effectively lower hypertension. Which type of many medications should be used initially for hypertension has been the subject of several large studies and various national guidelines.

The largest study, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), concluded that thiazide-type diuretics are better and cheaper than other major classes of drugs at preventing cardiovascular disease, and should be preferred as the starting drug. ALLHAT used the thiazide diuretic chlorthalidone. (ALLHAT showed that doxazosin, an alpha-adrenergic receptor blocker, had a higher incidence of heart failure events, and the doxazosin arm of the study was stopped.)

A subsequent smaller study (ANBP2) did not show the slight advantages in thiazide diuretic outcomes observed in the ALLHAT study, and actually showed slightly better outcomes for ACE-inhibitors in older white male patients.

Thiazide diuretics are effective, recommended as the best first-line drug for hypertension by many experts, and are much more affordable than other therapies, yet they are not prescribed as often as some newer drugs. Hydrochlorothiazide is perhaps the safest and most inexpensive agent commonly used in this class and is very frequently combined with other agents in a single pill. Doses in excess of 25 milligrams per day of this agent incur an unacceptable risk of low potassium or Hypokalemia. Patients with an exaggerated hypokalemic response to a low dose of a thiazide diuretic should be suspected to have Hyperaldosteronism, a common cause of secondary hypertension.

Other drugs have a role in treating hypertension. Adverse effects of thiazide diuretics include hypercholesterolemia, and impaired glucose tolerance with increased risk of developing Diabetes mellitus type 2. The thiazide diuretics also deplete circulating potassium unless combined with a potassium-sparing diuretic or supplemental potassium. Some authors have challenged thiazides as first line treatment. However as the Merck Manual of Geriatrics notes, "thiazide-type diuretics are especially safe and effective in the elderly."

Current UK guidelines suggest starting patients over the age of 55 years and all those of African/Afrocaribbean ethnicity firstly on calcium channel blockers or thiazide diuretics,

whilst younger patients of other ethnic groups should be started on ACE-inhibitors. Subsequently if dual therapy is required to use ACE-inhibitor in combination with either a calcium channel blocker or a (thiazide) diuretic. Triple therapy is then of all three groups and should the need arise then to add in a fourth agent, to consider either a further diuretic (e.g. spironolactone or furosemide), an alpha-blocker or a beta-blocker. Prior to the demotion of beta-blockers as first line agents, the UK sequence of combination therapy used the first letter of the drug classes and was known as the "ABCD rule".

The choice between the drugs is to a large degree determined by the characteristics of the patient being prescribed for, the drugs' side-effects, and cost. For example, asthmatics have been reported to have worsening symptoms when using beta blockers. Most drugs have other uses; sometimes the presence of other symptoms can warrant the use of one particular antihypertensive (such as beta blockers in case of tremor and nervousness, and alpha blockers in case of benign prostatic hyperplasia). The JNC 7 report outlines compelling reasons to choose one drug over the others for certain individual patients.

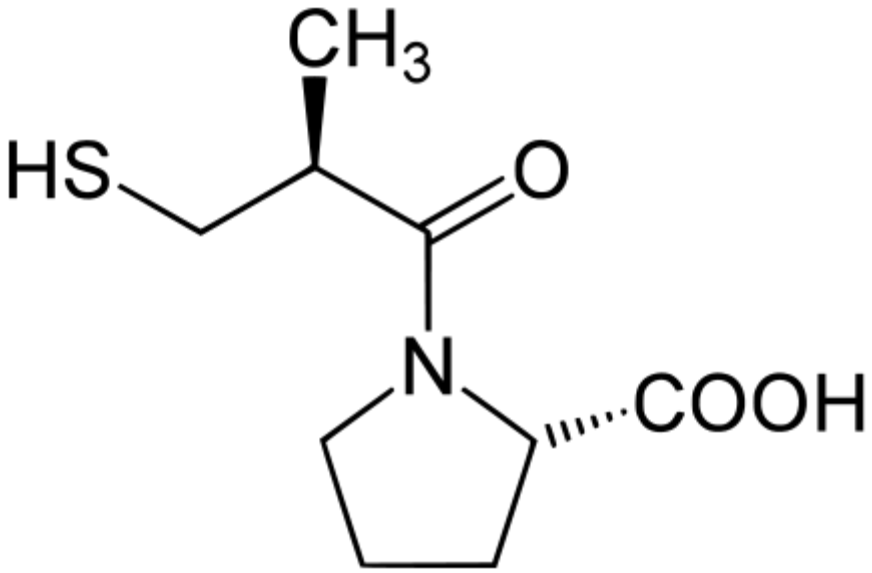
Non-drug treatment options

Several studies have found that hibiscus tea has a substantial antihypertensive effect attributable to the flower's ACE-inhibiting anthocyanin content, and possibly to a diuretic effect. One study found that hibiscus conferred an antihypertensive effect comparable to 50 mg./day of the drug captopril.

Another potential treatment is Coenzyme Q10, which a meta analysis of 12 studies found reductions in systolic pressure of 10-17 points and a reduction in diastolic pressure of 8-10 points with doses of roughly 200mg/day.

Chapter 18

ACE Inhibitor



Captopril, the first ACE inhibitor

ACE inhibitors or **angiotensin-converting enzyme inhibitors**, are a group of pharmaceuticals that are used primarily in treatment of hypertension and congestive heart failure.

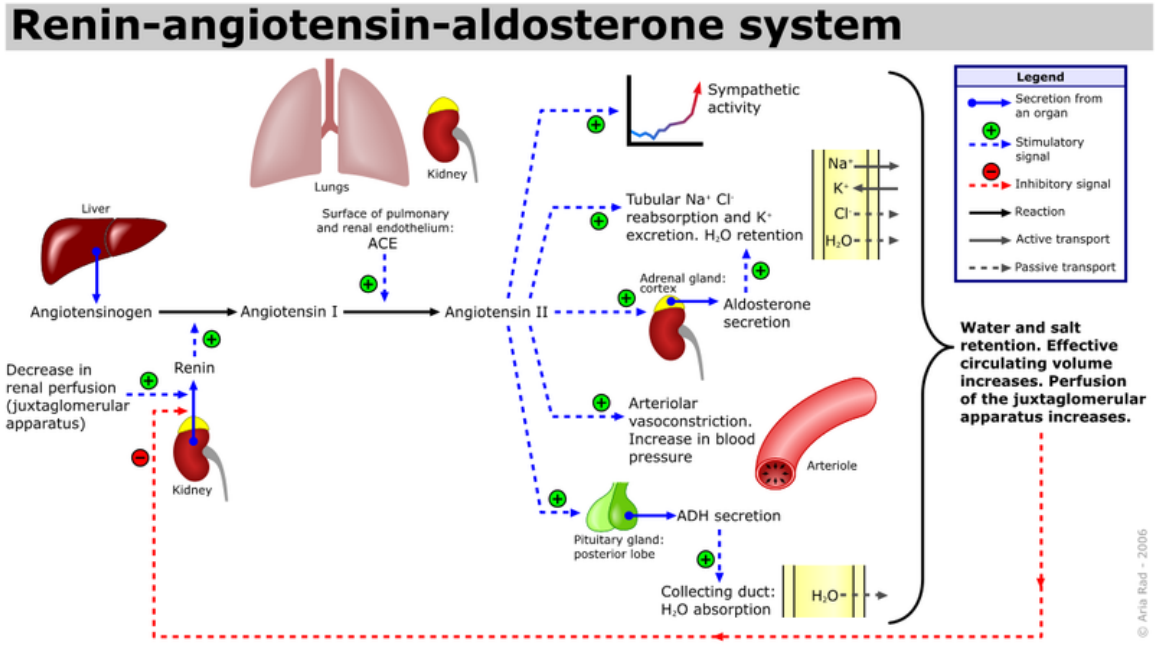
Clinical use

ACE inhibitors are used primarily in the treatment of hypertension, though they are also sometimes used in patients with cardiac failure, renal disease or systemic sclerosis ACEIs can also be used to treat diabetic nephropathy and left ventricular hypertrophy.

Mechanism of action

Angiotensin-converting enzyme inhibitors reduce the activity of the renin-angiotensin-aldosterone system.

The renin-angiotensin-aldosterone system (RAAS)



Renin-angiotensin-aldosterone system

One mechanism for maintaining the blood pressure is the release of a protein called **renin** from cells in the kidney (to be specific, the juxtaglomerular apparatus). This produces another protein called **angiotensin**, which signals the adrenal gland to produce a hormone called **aldosterone**. This system is activated in response to a fall in blood pressure (hypotension) as well as markers of problems with the salt-water balance of the body, such as decreased sodium concentration in a part of the kidney known as the distal tubule, decreased blood volume and stimulation of the kidney by the sympathetic nervous system. In such a situation, the kidneys release renin, which acts as an enzyme and cuts off all but the first 10 amino-acid residues of angiotensinogen (a protein made in the liver, and which circulates in the blood). These 10 residues are then known as angiotensin I. Angiotensin I is then converted to angiotensin II by angiotensin converting enzyme (ACE) which removes a further 2 residues and is found in the pulmonary circulation as well as in the endothelium of many blood vessels. The system in general aims to increase blood pressure by increasing the amount of salt and water the body retains, although angiotensin is also very good at causing the blood vessels to tighten (a potent vasoconstrictor).

Effects

ACE inhibitors block the conversion of angiotensin I to angiotensin II. They, therefore, lower arteriolar resistance and increase venous capacity; increase cardiac output, cardiac index, stroke work, and volume; lower renovascular resistance; and lead to increased natriuresis (excretion of sodium in the urine). Renin will increase in concentration in the blood due to negative feedback of conversion of AI to AII. Angiotensin I will increase for

the same reason. AII will decrease. Aldosterone will decrease. Bradykinin will increase due to less inactivation that is done by ACE enzyme.

Under normal conditions, angiotensin II will have the following effects:

- vasoconstriction (narrowing of blood vessels), which may lead to increased blood pressure and hypertension

  – constriction of the efferent arterioles of the kidney, leading to increased perfusion pressure in the glomeruli.

- Contribute to ventricular remodeling and ventricular hypertrophy of the heart.
- stimulation of the adrenal cortex to release aldosterone, a hormone that acts on kidney tubules to retain sodium and chloride ions and excrete potassium. Sodium is a "water-holding" molecule, so water is also retained, which leads to increased blood volume, hence an increase in blood pressure.
- stimulation of the posterior pituitary to release vasopressin (also known as anti-diuretic hormone (ADH)), which also acts on the kidneys to increase water retention.
- decrease renal protein kinase C.

With ACE inhibitor use, the effects of angiotensin II are prevented, leading to decreased blood pressure.

Epidemiological and clinical studies have shown that ACE inhibitors reduce the progress of diabetic nephropathy independently from their blood pressure-lowering effect. This action of ACE inhibitors is utilised in the prevention of diabetic renal failure.

ACE inhibitors have been shown to be effective for indications other than hypertension even in patients with normal blood pressure. The use of a maximum-dose of ACE inhibitors in such patients (including for prevention of diabetic nephropathy, congestive heart failure, prophylaxis of cardiovascular events) is justified because it improves clinical outcomes, independent of the blood pressure-lowering effect of ACE inhibitors. Such therapy, of course, requires careful and gradual titration of the dose to prevent the effects of rapidly decreasing blood pressure (dizziness, fainting, etc.).

ACE inhibitors have also been shown to cause a central enhancement of parasympathetic activity in healthy volunteers and patients with heart failure. This action may reduce the prevalence of malignant cardiac arrhythmias, and the reduction in sudden death reported in large clinical trials.

The ACE inhibitor enalapril has also been shown to reduce cardiac cachexia in patients with chronic heart failure. Cachexia is a poor prognostic sign in patients with chronic heart failure. ACE-inhibitors are now used to reverse frailty and muscle wasting in elderly patients without heart failure.

Adverse effects

Common adverse drug reactions include: hypotension, cough, hyperkalemia, headache, dizziness, fatigue, nausea, and renal impairment. There is also some evidence to suggest that ACE inhibitors might increase inflammation-related pain.

A persistent dry cough is a relatively common adverse effect believed to be associated with the increases in bradykinin levels produced by ACE inhibitors, although the role of bradykinin in producing these symptoms remains disputed by some authors. Patients who experience this cough are often switched to angiotensin II receptor antagonists.

Rash and taste disturbances, infrequent with most ACE inhibitors, are more prevalent in captopril and is attributed to its sulfhydryl moiety. This has led to decreased use of captopril in clinical setting, although it is still used in scintigraphy of the kidney.

Renal impairment is a significant adverse effect of all ACE inhibitors. The reason for this is still unknown. Some suggest that it is associated with their effect on angiotensin II-mediated homeostatic functions such as renal blood flow. Renal blood flow may be affected by angiotensin II because it vasoconstricts the efferent arterioles of the glomeruli of the kidney, thereby increasing glomerular filtration rate (GFR). Hence, by reducing angiotensin II levels, ACE inhibitors may reduce GFR, a marker of renal function. To be specific, ACE inhibitors can induce or exacerbate renal impairment in patients with renal artery stenosis. This is especially a problem if the patient is concomitantly taking an NSAID and a diuretic. When the three drugs are taken together, there is a very high risk of developing renal failure.

ACE inhibitors may cause hyperkalemia. Suppression of angiotensin II leads to a decrease in aldosterone levels. Since aldosterone is responsible for increasing the excretion of potassium, ACE inhibitors ultimately cause retention of potassium.

A severe allergic reaction that rarely can affect the bowel wall and secondarily cause abdominal pain can occur. This "anaphylactic" reaction is very rare as well.

Some patients develop angioedema due to increased bradykinin levels. There appears to be a genetic predisposition toward this adverse effect in patients that degrade bradykinin more slowly than average.

In pregnant women, ACE inhibitors taken during the first trimester have been reported to cause major congenital malformations, stillbirths, and neonatal deaths. Commonly reported fetal abnormalities include hypotension, renal dysplasia, anuria/oliguria, oligohydramnios, intrauterine growth retardation, pulmonary hypoplasia, patent ductus arteriosus, and incomplete ossification of the skull.

Contraindications and precautions

The ACE inhibitors are contraindicated in patients with:

- Previous angioedema associated with ACE inhibitor therapy
- Renal artery stenosis (bilateral, or unilateral with a solitary functioning kidney)
- Hypersensitivity to ACE inhibitors

ACE inhibitors should be used with caution in patients with:

- Impaired renal function
- Aortic valve stenosis or cardiac outflow obstruction
- Hypovolemia or dehydration
- Hemodialysis with high-flux polyacrylonitrile membranes

ACE inhibitors are ADEC Pregnancy category D, and should be avoided in women who are likely to become pregnant. In the U.S., ACE inhibitors are required to be labeled with a "black box" warning concerning the risk of birth defects when taking during the second and third trimester. It has also been found that use of ACE inhibitors in the first trimester is also associated with a risk of major congenital malformations, particularly affecting the cardiovascular and central nervous systems.

Potassium supplementation should be used with caution and under medical supervision owing to the hyperkalemic effect of ACE inhibitors.

Examples

ACE inhibitors can be divided into three groups based on their molecular structure:

Sulfhydryl-containing agents

- Captopril (trade name Capoten), the first ACE inhibitor
- Zofenopril

Dicarboxylate-containing agents

This is the largest group, including:

- Enalapril (Vasotec/Renitec)
- Ramipril (Altace/Tritace/Ramace/Ramiwin)
- Quinapril (Accupril)
- Perindopril (Coversyl/Aceon)
- Lisinopril (Listril/Lopril/Novatec/Prinivil/Zestril)
- Benazepril (Lotensin)

Phosphonate-containing agents

- Fosinopril (Monopril) is the only member of this group

Naturally occurring

- Casokinins and lactokinins are breakdown products of casein and whey that occur naturally after ingestion of milk products, especially cultured milk. Their role in blood pressure control is uncertain.
- The Lactotripeptides Val-Pro-Pro and Ile-Pro-Pro produced by the probiotic *Lactobacillus helveticus* or derived from casein have been shown to have ACE-inhibiting and antihypertensive functions.

Comparative information

All ACE inhibitors have similar antihypertensive efficacy when equivalent doses are administered. The main point-of-difference lies with captopril, the first ACE inhibitor, which has a shorter duration of action and increased incidence of certain adverse effects.

Certain agents in the ACE inhibitor class have been proven, in large clinical studies, to reduce mortality post-myocardial infarction, prevent development of heart failure, *etc.*. The ACE inhibitor most prominently recognized for these qualities is ramipril (Altace). Because ramipril has been shown to reduce mortality rates even among patient groups not suffering from hypertension, there are some (mostly drug-company representatives) who believe that ramipril's benefits may extend beyond those of the general abilities it holds in common with other members of the ACE inhibitor class.

ACEI equivalents

The ACE inhibitors have different strengths with different starting dosages. Dosage should be adjusted according to the clinical response.

ACE inhibitors dosages for hypertension

		Dosage		
Note: bid = 2 times a day, tid = 3 times a day, d = daily Drug dosages from Drug Lookup, Epocrates Online.				
Name	**Equivalent daily dose**	**Start**	**Usual**	**Maximum**
Benazepril	10 mg	10 mg	20–40 mg	80 mg
Captopril	50 mg (25 mg bid)	12.5–25 mg bid-tid	25–50 mg bid-tid	450 mg/d
Enalapril	5 mg	5 mg	10–40 mg	40 mg
Fosinopril	10 mg	10 mg	20–40 mg	80 mg
Lisinopril	10 mg	10 mg	10–40 mg	80 mg
Moexipril	7.5 mg	7.5 mg	7.5–30 mg	30 mg

Name	Equivalent daily dose	Start	Usual	Maximum
Perindopril	4 mg	4 mg	4–8 mg	16 mg
Quinapril	10 mg	10 mg	20–80 mg	80 mg
Ramipril	2.5 mg	2.5 mg	2.5–20 mg	20 mg
Trandolapril	2 mg	1 mg	2–4 mg	8 mg

Note: bid = 2 times a day, tid = 3 times a day, d = daily
Drug dosages from Drug Lookup, Epocrates Online.

ACE inhibitors dosages for hypertension

Angiotensin II receptor antagonists

ACE inhibitors possess many common characteristics with another class of cardiovascular drugs called angiotensin II receptor antagonists, which are often used when patients are intolerant of the adverse effects produced by ACE inhibitors. ACE inhibitors do not completely prevent the formation of angiotensin II, as there are other conversion pathways, and so angiotensin II receptor antagonists may be useful because they act to prevent the action of angiotensin II at the AT_1 receptor, leaving AT_2 receptor unblocked; the latter may have consequences needing further study.

Use in combination

The combination therapy of angiotensin II receptor antagonists with ACE inhibitors may be superior to either agent alone. This combination may increase levels of bradykinin while blocking the generation of angiotensin II and its activity at the AT_1 receptor. This 'dual blockade' may be more effective than using an ACE inhibitor alone, because angiotensin II can be generated via non-ACE-dependent pathways. Preliminary studies suggest that this combination of pharmacologic agents may be advantageous in the treatment of essential hypertension, chronic heart failure, and nephropathy. However, more studies are needed to confirm these highly preliminary results. While statistically significant results have been obtained for its role in treating hypertension, clinical significance may be lacking.

Patients with heart failure may benefit from the combination in terms of reducing morbidity and ventricular remodeling.

The most compelling evidence for the treatment of nephropathy has been found: This combination therapy partially reversed the proteinuria and also exhibited a renoprotective effect in patients afflicted with diabetic nephropathy, and pediatric IgA nephropathy.

History

The first step in the development of (ACE) inhibitors was the discovery of angiotensin-converting enzyme (ACE) in plasma by Leonard T. Skeggs and his colleagues in 1956. Brazilian scientist Sergio Ferreira reported in 1965 of a 'bradykinin-potentiating factor

(BPFs) present in the venom of bothrops jararaca, a South American pit viper. Dr SH Ferreira then proceeded to John Vanes laboratory as a Post-Doc with his already-isolated BPFs. The conversion of the inactive angiotensin I to the potent angiotensin II was thought to take place in the plasma. However, in 1967, Kevin K. F. Ng and John R. Vane showed that the plasma (ACE) is too slow to account for the conversion of angiotensin I to angiotensin II *in vivo*. Subsequent investigation showed that rapid conversion occurs during its passage through the pulmonary circulation.

Bradykinin is rapidly inactivated in the circulating blood and it disappears completely in a single passage through the pulmonary circulation. Angiotensin I also disappears in the pulmonary circulation due to its conversion to angiotensin II. Furthermore, angiotensin II passes through the lungs without any loss. The inactivation of bradykinin and the conversion of angiotensin I to angiotensin II in the lungs was thought to be caused by the same enzyme. In 1970, Ng and Vane using bradykinin potentiating factor (BPF) provided by Sérgio Henrique Ferreira showed that the conversion of angiotensin I to angiotensin II is inhibited during its passage through the pulmonary circulation.

Bradykinin-potentiating factor (BPF) is derived from the venom of the pit viper (*Bothrops jararaca*). It is a family of peptides, whose potentiating action is linked to inhibition of bradykinin by ACE. Molecular analysis of BPF yielded a nonapeptide BPF teprotide (SQ 20,881), which showed the greatest (ACE) inhibition potency and hypotensive effect *in vivo*. Teprotide had limited clinical value, due to its peptide nature and lack of activity when given orally. In the early 1970s, knowledge of the structure-activity relationship required for inhibition of ACE was growing. David Cushman, Miguel Ondetti, and colleagues used peptide analogues to study the structure of ACE, using carboxypeptidase A as a model. Their discoveries led to the development of captopril, the first orally-active ACE inhibitor in 1975.

Captopril was approved by the United States Food and Drug Administration in 1981. The first non-sulfhydryl-containing (ACE) inhibitor enalapril was marketed two years later. Since then, at least twelve other ACE inhibitors have been marketed.

In 1991, Japanese scientists created the first ever milk-based ACE inhibitor in the form of a fermented milk drink, using specific cultures to liberate the IPP from the dairy protein. It is interesting to note that Val-Pro-Pro is also liberated in this process—another milk tripeptide with a very similar chemical structure to IPP. Together, these peptides are now often referred to as lactotripeptides. Shortly after this, in 1996, the first human study confirmed the blood pressure-lowering effect of IPP in fermented milk. Although twice the amount of VPP is needed to achieve the same ACE inhibiting activity as the originally discovered IPP, it is assumed that VPP also adds to the total blood pressure lowering effect. Since the first lactotripeptides discovery, more than 20 human clinical trials have been conducted in many different countries.