REVIEW OF LITERATURE

Epidemiology :

The prevalence of diabetes is rapidly rising all over the globe at an alarming rate.[18] Over the past 30 yrs, the status of diabetes has changed from being considered as a mild disorder of the elderly to one of the major causes of morbidity and mortality affecting the youth and middle aged people. It is important to note that the rise in prevalence is seen in all six inhabited continents of the globe.[19] Although there is an increase in the prevalence of type 1 diabetes also, the major driver of the epidemic is the more common form of diabetes, namely type 2 diabetes, which accounts for more than 90 per cent of all diabetes cases. Nowhere is the diabetes epidemic more pronounced than in India as the World Health Organization (WHO) reports show that 32 million people had diabetes in the year 2000. The International Diabetes Federation (IDF) estimates the total number of diabetic subjects to be around 40.9 million in India and this is further set to rise to 69.9 million by the year 2025.[20]

The first national study on the prevalence of type 2 diabetes in India was done between 1972 and 1975 by the Indian Council Medical Research (ICMR, New Delhi).[4] Screening was done in about 35,000 individuals above 14 yr of age. The prevalence was 2.1per cent in urban population and 1.5 per cent in the rural population while in those above 40 yr of age, the prevalence was 5 per cent in urban and 2.8 percent in rural areas.[21] Subsequent studies showed a rising trend in the prevalence of diabetes across different parts of India. In 1988, a study done in a small township in south India reported a prevalence of 5 percent.[22] A national rural diabetes survey was done between 1989 and 1991 in different parts of the country in selected rural populations. This study which used the 1985 WHO criteria to diagnose diabetes, reported a crude prevalence of 2.8 per cent.[23] A study done in

1988 in Chennai reported a prevalence of 8.2 per cent in the urban and 2.4 per cent in the rural areas.[24] A subsequent study in the same urban area done after five years showed an age standardized prevalence of 11.6 per cent indicating a rising trend in prevalence of diabetes.[25] A very high prevalence of 16.3 per cent was reported in Thiruvanathapuram in Kerala State in the year 199910. In the same year, a prevalence of 8.2 per cent was reported from Guwahati. A cross-sectional population survey was done in the Kashmir valley in 2000 and the prevalence of 'known diabetes' among adults aged >40 yr was found to be 1.9 percent.[26]

The dramatic rise in the prevalence of type 2 diabetes and related disorders like obesity, hypertension and the metabolic syndrome could be related to the rapid changes in life style that has occurred during the last 50 yr. Although this "epidemiological transition", which includes improved nutrition, better hygiene, control of many communicable diseases and improved access to quality healthcare have resulted in increased longevity. It has also led to the rapid rise of the new age diseases like obesity, diabetes and heart disease.

The intrusion of western culture into the lives of traditional indigenous communities has also had devastating results in terms of the rise in diabetes and related metabolic disorders. In virtually all populations, higher fat diets and decreased physical activity and sedentary occupational habits have accompanied the process of modernization which has resulted in the doubling of the prevalence of obesity and type 2 diabetes in less than a generation.

The 'fast food culture' which has overwhelmed our cities and towns is also a major driver of the diabetes epidemic. The 'fast-foods' that are fat and calorie rich are easily available in the numerous food joints. As a majority of the immigrants in Indian cities

depend on these unhealthy 'junk' foods, this may be a major factor in the rising prevalence of diabetes and cardiovascular diseases in urban slums.[26]

Urban rural differences in the prevalence of diabetes have been consistently reported from India. ICMR study (1972-1975) reported that the prevalence was 2.1 per cent in urban and 1.5 per cent in rural areas, a later study showed that the prevalence was three times higher among the urban (8.2%) compared to the rural population 2.4%).[24] A study done in southern Kerala looked at the variations in the prevalence of type 2 diabetes among different geographic divisions within a region.[21] The prevalence of diabetes was the highest in the urban (12.4%) areas, followed by the midland (8.1%), highland (5.8%) and coastal division (2.5%).[27] The prevalence of diabetes is now rapidly increasing among the poor in the urban slum dwellers, the middle class and even in the rural areas. This is due to rapid changes in physical activity and dietary habits even among the poorer sections of the society.[28]

The early identification of at risk individuals and appropriate intervention in the form of weight reduction, changes in dietary habits and increased physical activity could greatly help to prevent, or at least delay, the onset of diabetes and thus reduce the burden due to non communicable diseases in India.[26]

Pathogenesis of diabetes:

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels.

Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the β-cells of the pancreas with consequent insulin

deficiency to abnormalities that result in resistance to insulin action. The basis of the abnormalities in carbohydrate, fat, and protein metabolism in diabetes is deficient action of insulin on target tissues. Deficient insulin action results from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action. Impairment of insulin secretion and defects in insulin action frequently coexist in the same patient, and it is often unclear which abnormality, if either alone, is the primary cause of the hyperglycemia.

Four polypeptides with hormonal activity are secreted by the islets of Langerhans in the pancreas, namely insulin, glucagon, somatostatin and pancreatic polypeptide. The A cells secrete glucagon, B cells insulin, D cells somatostatin and F cells secrete pancreatic polypeptide.

Like other polypeptide hormones and related proteins that enter the endoplasmic reticulum, insulin is synthesized as part of a longer preprohormone. The gene for insulin is located on the short arm of chromosome 11 in humans. It is synthesized in the rough endoplasmic reticulum of the β-cells. It is then transported to the Golgi apparatus, where it is packed in membrane bound granules. These granules move to the plasma membrane by a process involving microtubules, and their contents are expelled by exocytosis. The insulin then crosses the basal laminas of the β-cell and a neighboring capillary and the fenestrated endothelium of the capillary to reach the bloodstream.[1]

Definition

Glycogen is a form of stored glucose that the body uses as an energy source. Glycogen storage disease (GSD) involves defects that cause an abnormal accumulation of glycogen, usually found in the liver, muscle, or both. When accumulation occurs in the liver,

glycogen storage diseases result in liver enlargement and in conditions ranging from mild hypoglycemia to liver failure. When the accumulation occurs in muscle, glycogen storage diseases result in conditions ranging from difficulty exercising to cardiac and respiratory failure.

Description

Glucose is a simple sugar that functions as a critical energy source for most bodily functions. Glucose can be acquired through the diet or formed within the bodily cells. Levels of glucose in the blood are maintained in a very narrow range, before and after the ingestion of food. Eating a meal supplies a high level of dietary glucose. Hormones, such as insulin, assist in the removal of glucose from the blood and into cells to be used as energy. Excess glucose is accumulated in the form of glycogen as a type of easily mobilized energy storage for use when food is not plentiful. Even while sleeping, glycogen stores are available to maintain blood glucose levels and energy for life.

The process of the formation of glycogen sheets is termed glycogenesis, and is stimulated by hormones, such as insulin. The process of the breakdown of sheets of glycogen into usable glucose is termed glycogenolysis, and is also under tight control. Hormones that stimulate glycogenolysis control enzymes to remove only the necessary amount of glucose from glycogen stores. With an average daily food intake, glycogen stores are constantly being built up and broken down based on the needs of the body. Average glycogen stores serve as a short-term supply of glucose, and need to be replenished daily. Glycogen serves as energy storage in every organ, but the liver and skeletal muscles are the main sites of glycogen deposition. The brain is dependent upon glucose for energy, and so requires a certain level of blood glucose to be available at all times. Because the brain has

only minimal glycogen stores, it is mainly dependent on glycogen from other organs, such as the liver.

Glycogen has separate functions in liver and muscle. Muscle uses glycogen as a fuel source with which to produce energy during activity. As muscle is being used, glycogen stores are being broken down into glucose, turned into cellular energy called ATP, and depleted. In the liver, glycogen is mainly used as a maintenance energy source for the entire body, and is responsible for keeping blood glucose levels in a stable range. After ingestion of dietary glucose, the liver takes up many food breakdown products from the bloodstream, converts them into glucose, and stores them as glycogen. Sometime after a meal, when blood glucose levels naturally fall, the liver uses its glycogen stores to replenish the blood with glucose. Organs that cannot create enough glycogen of their own are thus supplied.

Glycogen storage diseases may involve defects in glycogen breakdown or formation in muscle, liver, or both muscle and liver. Some classic features of GSDs that primarily involve muscle are muscle cramps, exercise intolerance, and easy fatigability. Some classic features of GSDs that primarily involve liver are liver enlargement, liver function defects, and hypoglycemia. Most GSDs can have subtypes with onset at different stages of life. There are many types of GSD that involve different defects in glycogen utilization. The types of GSD that are best described are types I through VIII, each with a distinct name and Glycogen is the principal storage form of loose (glucose) in animal cells, though it is also found in various species of microorganisms, such as bacteria and tuna. It is a large, branched polymer of linked glucose residues (portions of larger molecules) that can be readily mobilized as an energy source, increasing the amount of glucose immediately available to the organism [29] during muscular activity. Since the brain relies

on glucose as its preferred fuel, the ability to maintain a steady supply of glucose, which is the major sugar circulating in the blood of higher animals, is crucial to survival.

Glycogen is found in the form of granules in the cytosol, the internal fluid of the cell. About three-fourths of the body's glycogen supply is stored in muscle cells. However, liver cells (hepatocytes) have the highest concentration of glucose (a maximum of approximately eight percent in liver versus one percent of the muscle mass of an adult male human being). Small amounts of glycogen are also found in the kidneys, and even smaller amounts in certain glial cells in the brain and in white blood cells.

The physiological role of glycogen depends on the type of cell in which it is stored[31]

- Liver cells play a key role in regulating the blood glucose level as they can either break down glycogen (glycogenolysis) to release glucose into the blood or withdraw glucose from the blood and store it by synthesizing glycogen (glycogenesis). It is noteworthy that glucose is not a major fuel for the liver, which mainly utilizes keto acids. The liver cells, therefore, perform the glucose storage and release primarily for the benefit of other organs. This reflects the principle of dual purposes, whereby the components of living organisms work together harmoniously because they not only exhibit an individual purpose oriented toward their own self-maintenance and development, but also serve a purpose for the whole.
- In skeletal muscle, glycogen is an energy reserve that can be tapped during exercise. Muscle cells lack the ability to release glucose into the blood, so their glycogen store is destined for internal use, powering muscle contraction during strenuous activity.

  Glycogen-storage disorders are a type of inherited metabolic disease resulting from deficiencies of the enzymes that participate in glycogen metabolism. Symptoms vary

in type and severity, ranging from exercise intolerance to low blood sugar and kidney disease. Certain forms of glycogen storage disorders cause cardio-respiratory failure or liver failure in affected infants.[30]

The structure of glycogen: Most glucose residues are linked by a-1,4 glycosidic bonds . Approximately one in ten glucose residues form a-1,6 glycosidic bonds, creating a branched structure. The non-reducing end-branches facilitate glycogen's interaction with enzymes involved in its synthesis and breakdown.[31]

Glycogen is a highly branched polymer of about 30,000 glucose residues. It has a molecular weight between 106 and 107 Daltons. Given its size, glycogen is considered a polysaccharide: i.e., a large carbohydrate constructed out of hundreds or thousands of linked monosaccharides (such as glucose).

Linking the monosaccharide components of glycogen are glycosidic bonds, chemical bonds that form between the hemiacetal group of a saccharide and the hydroxyl group of an alcohol. Specifically most of the glucose units are linked by a-1, 4 bonds, in which the carbon-1 of one sugar molecule is linked to the carbon-4 of the adjacent molecule. In the alpha configuration, the oxygen atom is located below the plane of the sugar ring.

Approximately one in ten glucose residues also forms an a-1, 6 glycosidic bond with an adjacent glucose, which results in the creation of a branch. Glycogen has only one reducing end and a large number of non-reducing ends with a free hydroxyl group at carbon-4. The branches increase the solubility of glycogen and make its sugar units accessible to the enzymes involved in glycogen metabolism, which nest between the outer branches of the glycogen molecules and act on the non-reducing ends. Therefore, the many end-branches of

glycogen facilitate its rapid synthesis and breakdown, making it a readily mobilized source of energy.

Starch, which plays a similar energy-storage role in plants, can also exist in a branched form called amylopectin, though it has a lesser degree of branching than glycogen (about one in 30 glucose residues form a-1, (bonds). In contrast, cellulose, the other major polysaccharide in plants, is an unbranched polymer of glucose, in which 3-1,4 linkages form very long, straight chains. This closed structure is suited to the structural role of cellulose, a major component of plant cell walls, whereas the open helices of glycogen and starch, which are nutritional molecules, provide easy access to stored glucose. [31]

Glycogen in liver functions to maintain blood sugar levels

The liver is a major control site of blood glucose levels, it responds to hormonal signals that indicate reduced or elevated amounts of glucose in the blood. The synthesis and breakdown of glycogen in the liver thus serves as a means for maintaining a steady supply of fuel for organs such as the brain, allowing glucose to be stored or released depending on the energy needs of the organism.

As a carbohydrate meal is eaten and digested, blood glucose levels rise, and the pancreas secretes the hormone insulin. The hepatic portal vein delivers glucose-rich blood from the digestive system to the liver's hepatocytes; insulin, also carried in the blood, acts on the hepatocytes to stimulate the action of several enzymes, including glycogen synthase, involved in the synthesis of glycogen. Glucose molecules are added to the chains of glycogen for as long as both insulin and glucose remain plentiful. In this postprandial or "fed" state, the liver takes in more glucose from the blood than it releases.

The hormones glucagon, produced by the pancreas, and epinephrine, secreted by the adrenal gland, serves in many respects as a counter-signal to insulin. When blood glucose levels begin to fall (about four hours after a meal), they stimulate the breakdown of glycogen. The freed glucose is then released from the liver into the blood. For the next eight to 12 hours (for example, during an overnight fast), glucose derived from liver glycogen will be the primary source of blood glucose to be used by the rest of the body for fuel.

Although liver cells maintain a high concentration of glycogen, the liver meets most of its own energy needs through keto acids derived from the breakdown of amino acids. The liver's role in glycogen metabolism is to synthesize and degrade glycogen for the benefit of the organism as a whole.

Glycogen in muscle is an energy reserve for strenuous exercise

Muscle cells lack the enzyme glucose-6 phosphatase, which is the enzyme that enables liver cells to export glucose into the blood. Therefore, the glycogen stored in muscle cells is utilized internally rather than shared. Other cells that contain small amounts of glycogen use it locally as well.

Glycogen in muscle cells functions as an immediate source of available glucose during bursts of activity, such as a 100-meter sprint. When the energy needs of the cell outpace its limited oxygen supply, AT P (the "energy currency" of the cell) is produced in part by the anaerobic glycolysis of glucose derived from muscle glycogen. Glycolysis is a metabolic pathway by which glucose may be broken down to pyruvate in the absence of oxygen. Although the complete oxidation of glucose in the presence of oxygen (oxidative phosphorylation) produces about 18 times the amount of ATP, glycolysis occurs at a rate approximately 100 times faster than aerobic respiration. During a period of brief, intense

exertion, the energy requirement is to generate the maximum amount of ATP for muscle contraction in the shortest time frame. However, a longer period of activity requires at least the partial use of ATP derived from oxidative phosphorylation, which explains the slower pace of a 1,000-meter run.

A description of the Cori cycle

Animals can convert glucose 6-phosphate to glucose, which is secreted into the circulatory system. Mammals, in particular, have a sophisticated cycle of secretion and uptake of glucose. It's called the Cori cycle after the Nobel Laureates: Carl Ferdinand Cori and Gerty Theresa Cori.[32]

The liver may also work in tandem with skeletal muscle in times of exertion. The Cori cycle refers to the recycling of lactate or lactic acid produced by muscle during anaerobic metabolism. The lactate is converted to glucose by the liver. This permits the regeneration of NAD+ required for glycolysis to continue. The lactate diffuses into the blood and is taken up by the liver, which oxidizes it back to pyruvate. Most of the pyruvate is then converted to glucose (via gluconeogenesis). The six carbon molecule, glucose, is split into two 3-carbon molecules (lactate) that are then converted to another 3-carbon molecule (pyruvate). Two pyruvates are joined to make glucose.[33]

This glucose circulates in the blood, where it can be used by muscles if needed or stored as glycogen. The Cori cycle allows the muscles to continue focusing exclusively on the production of ATP while the liver handles the lactate produced in muscle. The cycle also prevents lactate acidosis by removing lactate from the blood. Otherwise, pH would fall as the buffering capacity of blood is exceeded.

Glycogen and marathon running

Since the human body is unable to hold more than approximately 2,000 kcal of glycogen, marathon runners commonly experience a phenomenon referred to as "bonking" or "hitting the wall" around the 20-mile (32-km) point of a marathon. Symptoms of this condition, which signals the depletion of glycogen stores, include general weakness, fatigue, and manifestations of hypoglycemia (low blood sugar), such as dizziness and even hallucinations. This rapid drop in performance results from a shift in the fuel supply: as glycogen stores diminish, ATI' must also be generated in part from iat1, acid oxidation, which is a slower process than the oxidation of glycogen. The simultaneous utilization of both fuels allows for a balance between endurance and speed, preserving enough glucose to fuel the runner's final push to the finish line.

There are several approaches available to prevent glycogen depletion during a marathon or another endurance exercise such as cycling:

- Carbohydrate loading is used to ensure that the initial glycogen level is maximized. This technique consists of increasing the intake of complex carbohydrates in the final three days preceding the event.
- Consuming food or drink that contains carbohydrates during the exercise will replenish the supply of glucose. This is a requirement for very long distances; it is estimated that Tour de France competitors receive up to 50 percent of their daily caloric intake from on-the-bike supplements.
- Decreasing the intensity of the exercise to the so-called "fat-loss" level (a heart rate of 130 beats per minute for a 30-year-old athlete) will lower both the energy requirements per unit of distance and the fraction of the energy that comes from glycogen.

Disorders of glycogen metabolism

The most common disease involving abnormal glycogen metabolism is diabetes mellitus, which is characterized by persistent variable hyperglyceimia (high blood sugar levels), resulting either from a deficiency of insulin or from an inadequate response by the body's cells to insulin. As mentioned above, insulin is the principal control signal for the conversion of glucose to glycogen for storage in liver and muscle cells. Lowered insulin levels result in the reverse conversion of glycogen to glucose by the liver while blood sugar levels fall. With the system out of balance, the liver then releases more glucose into the blood than can be utilized by other cells.

Several inborn errors of metabolism are caused by inherited genetic deficiencies of the enzymes involved in glycogen synthesis or breakdown. Collectively referred to as glycogen storage diseases, they include the following types:

- Von Gierke's disease (Type I) is the most common of the glycogen storage diseases. It results from a deficiency of the enzyme glucose-6-phosphatase, which in turn impairs the ability of the liver to produce free glucose from glycogen stores and through gluconeogenesis. Since these are the two primary metabolic mechanisms by which the liver supplies glucose to the rest of the body during periods of fasting, hypoglycemia is symptomatic of the disease. Reduced glycogen breakdown results in increased glycogen storage in liver and kidneys, causing enlargement of both organs. Frequent or continuous feedings of cornstarch or other carbohydrates is the principal treatment.
- Pompe disease (Type II) is caused by a deficiency in a lysosome-specific enzyme of glycogen breakdown called acid alpha-glucosidase (GAA). It is the only glycogen storage disease involving a defect in the lysosome, an organelle that contains digestive

enzymes that breakdown macromolecules such as glycogen. The resulting build-up of glycogen causes progressive muscle weakness (myopathy) throughout the body and affects various body tissues, particularly in the heart, skeletal muscles, liver, and nervous system.

- A disorder involving glycogen metabolism in muscle is McArdle's disease (Type V). It is characterized by a deficiency of myophosphorylose, the muscle isoform of the enzyme glycogen phosphorylase. This enzyme participates in the breakdown of glycogen so that it can be utilized within the muscle cell. Persons with this disease experience difficulty when their muscles are called upon to perform relatively brief yet intense activity. The inability to break down glycogen into glucose leads to an energy shortage within the muscle, resulting in muscle pain and cramping, and sometimes causing serious injury to the muscles. In addition, the breakdown of muscle tissue can indirectly lead to kidney damage. Anaerobic exercise must be avoided but gentle aerobic activity is beneficial.

Structure of Insulin hormone :

Insulin is a polypeptide containing two chains of aminoacids linked by disulfide bridges. Minor difference in the aminoacid composition is noted from species to species.[1]

Biosynthesis and secretion:

In humans the gene of insulin is located on the short arm of chromosome 11.

It is synthesized in rough endoplasmic reticulum of β-cells. Like other polypeptide hormones, it is synthesized as a part of a larger preprohormone. Preproinsulin has a 23 amino acid signal peptide removed as it enters endoplasmic reticulum. The remainder of the molecule is then folded and the disulfide bonds are formed to make proinsulin. The peptide segment connecting the A and B chains, the Connecting peptide(C-peptide) facilitates the

folding and then is detached in the granules before secretion. It is then transported to Golgi apparatus, where it is packed in membrane bound granules. These moves to the plasma membrane by a process involving microtubules and their contents are expelled by exocytosis. Normally 90-97% of the product released from the β-cells is insulin along with equimolar amounts of c- peptide. The rest is mostly proinsulin. The insulin then crosses the basal laminas of the β-cells and a neighboring capillary and the fenestrated endothelium of the capillary to reach the blood stream. The half life of insulin in circulation in humans is about 5 minutes. It binds to insulin receptors and some is internalized.

The physiologic effects of insulin are both far reaching and complex. Though the hormone has rapid, intermediate and delayed actions, the best known is the hypoglycemic effect. The cause of clinical diabetes is always due to deficiency of the effects of insulin at the tissue level, but the deficiency may be relative. One of the common forms type-1(Insulin Dependent Diabetes Mellitus IDDM) is due to insulin deficiency caused by auto-immune destruction of B-cells in pancreatic islets, the A, D and F cells remain intact.[1]

Principle actions of insulin are divided into;rapid, Intermediate and Delayed

Rapid actions (in seconds) : Increased transport of glucose, aminoacids and K ion into insulin sensitive cells.

Intermediate: Stimulation of protein synthesis

Inhibition of protein degradation

Activation of glycolytic enzymes and glycogen synthase.

Inhibition of phosphorylase and gluconeogenic enzymes.

Delayed: Increase in mRNAs for lipogenic and other enzymes.

Mechanism of action of insulin:

The gene for insulin receptor has 22 exons, in humans is located on chromosome 19.Insulin receptors are found on many different cells in the body, including cells in which insulin does not increase glucose uptake.

The insulin receptor, which has molecular weight of approximately 340000 is a tetramer made up of two α and two β glycoprotein subunits. All these are synthesized on a single m RNA and then proteolytically separated and bound to each other by disulfide bonds. The α subunits bind insulin and are extracellular, whereas the β span the membrane. The intracellular portions of the β subunits have tyrosine kinase activity. The α and β subunits are both glycosylated with sugar residues extending into the interstitial fluid. Binding of insulin triggers the tyrosine kinase activity of the β subunits, producing autophoshporylation of the β subunits on tyrosine residues. The autoposphorylation which is necessary for insulin to exert its biologic effects, triggers posphorylation of some Cytoplasmic proteins and deposphorylation of others, mostly on serine and threonine residues. Four related Insulin Receptor Substrate (IRS) have been described. IRS I, II, III and IV. When insulin binds to receptor, they aggregate in patches, are taken into the cell by receptor mediated endocytosis. Eventually the insulin –receptor complexes enter lysosomes, where the receptors are broken down or recycled. The half life of insulin receptor is about 7 hours.

The number or the affinity or both of insulin receptors is affected by insulin and other hormones, exercise, food and other factors. Exposure to increased amounts of insulin decreases receptor concentration and exposure to decreased insulin levels increases the number of receptors.[1]

Effects of secreted insulin:

Apart from its additional effects on amino acid and electrolyte transport, action on many enzymes and growth, the net effect of the hormone is storage of carbohydrate, protein and fat. The anabolic nature of hormone which increases the storage of glucose, fatty acids and amino acids is made to call the hormone "the hormone of abundance". The constellation of abnormalities caused by insulin deficiency is called "diabetes mellitus".[1]

The cause of clinical diabetes is always due to deficiency of the effects of insulin at the tissue level, but the deficiency may be relative. One of the common forms type-1 (**Insulin Dependent Diabetes Mellitus IDDM)** is due to insulin deficiency caused by auto-immune destruction of B-cells in pancreatic islets, the A, D and F cells remain intact**.**[34]

Type 1 diabetes (β-cell destruction, usually leading to absolute insulin deficiency)

Immune-mediated diabetes : Type1 diabetes: This was previously called juvenile diabetes, accounts for 5-10%of all cases of diabetes. Recent studies indicate that there are two subgroups of type1 diabetes. The most common being type1A, caused by autoimmune destruction of beta cells.Type1B is associated with severe insulin deficiency but without evidence of autoimmunity**.**

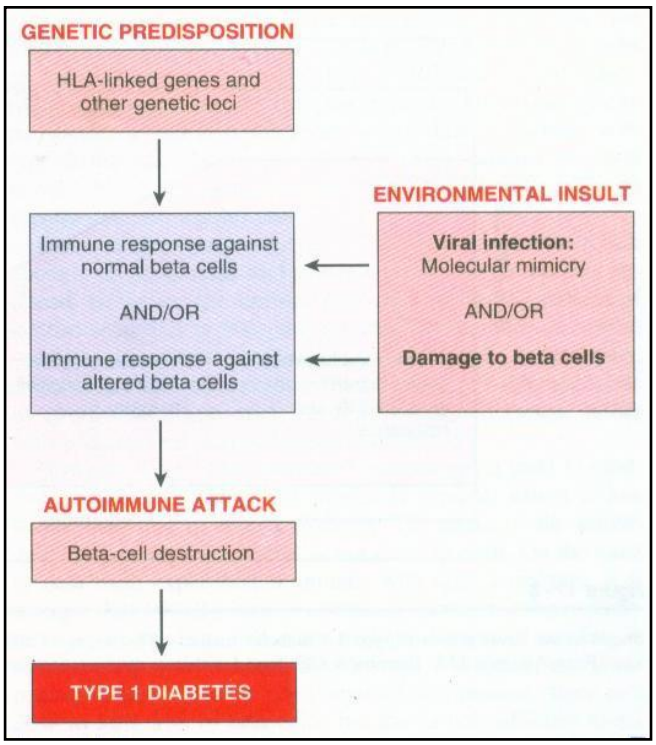
Pathogenesis: This form of diabetes results from an autoimmune destruction of β-cells. A severe insulin requiring form of type1A diabetes usually develops in children and adolescents, but this disease may manifest in adults in a milder, initially non-insulin-requiring form, which is called Latent Autoimmune diabetes in Adults. (LADA).Young Type1A patients depend on Insulin for survival and hence the term Insulin dependent diabetes mellitus was used earlier. Without insulin they develop serious metabolic complications such as acute ketoacidosis and coma.[34]

Three interlocking mechanisms are responsible for the islet cell destruction.

Gene susceptibility

Autoimmunity

An environmental insult.



1. Genetic susceptibility is linked to specific alleles of class ii major histocompatibility complex. (MHC) and other genetic loci that predispose certain persons to the development of autoimmunity against beta cells of the islets.
2. The auto immune reaction either develops spontaneously or is triggered by environmental event.
3. An environmental event that alters beta cells, rendering them immunogenic. Overt disease occurs after most of the beta cells have been destroyed.

Genetic Susceptibility: Type 1A is known to occur most frequently in persons descending from Northern European descent. The disease can aggregate in families about 6% of

offspring of people with this type of diabetes develop the disease. However about 80% of new cases occur without any family history and in identical twins the concordance rate is only 40%.Thus both genetic and environmental factors seem to play an important role.

Genome wide scans have reveled association of chromosome 6p21, where the MHC class II genes map. This locus is termed IDDM1 and accounts for about 45% of genetic susceptibility to this disease. Genes within this region provide both susceptibility and resistance to type 1A diabetes. Within the MHC class II region, the strongest disease linkage is to specific alleles of HLA –DQA1 and HLA DQB1 genes. Certain MHC class II genes (HLADR2 specificities) provide protection against diabetes. However protection is dominant over susceptibility. The mechanisms by which HLADR or DQ genes influence susceptibility to type 1A diabetes are not clear. It is known that the T –cell receptor of CD4+ T lymphocytes recognizes an antigen only after the peptide fragment of the antigen binds to the MHC class II molecule on the surface of antigen presenting cell. It is possible that the genetic variations in the MHC class II molecule that affect the antigen binding cleft may allow the presentation of self antigen to auto reactive CD4+ T cells. Thus class II MHC genes may affect the degree of immune responses to a pancreatic beta cell auto antigen or beta cell an auto antigen may be presented in a manner that promotes an abnormal immunologic reaction.[34]

Autoimmunity: Although this type of diabetes occurs abruptly, infact it results from a chronic autoimmune attack against beta cells that usually exists for years before disease onset. The classic manifestations of the disease like hyperglycemia result only after more than 90% of the beta cells have been destroyed.

- A lymphocyte rich inflammatory infiltrate, often intense is frequently observed in the islets of these patients early in the course of the disease. The infiltrate mainly consists of CD8+ T lymphocytes, with varying numbers of CD4+ lymphocytes and macrophages. Further, T lymphocytes from diseased animals can transfer diabetes to normal animals, thus establishing the primacy of T- cell mediated autoimmunity in type 1 diabetes.
- Islet beta cells are selectively destroyed, with preservation of other cell types. Cytotoxic CD8 + lymphocytes appear to kill islets either through release of cytotoxic granules or by inducing Fas mediated apoptosis.
- Auto antibodies to islet cell antigens indicate a risk for type1 diabetes. They appear as early as 9 months age and are present in 80% of the patients with new onset disease. The auto antibodies react against intracellular antigens such as glutamic acid decarboxylase, Insulin and several other Cytoplasmic proteins. In addition the peripheral blood T – cell responses to these same target antigens.
- Asymptomatic relatives of patients with type1 A diabetes develop islet cell autoantibodies months to years before they manifest the overt disease.
- Approximately 10-20% of patients who have type1 diabetes also have other organ specific autoimmune disorders.[34]

Environmental Factors:

In this form of diabetes, the rate of β-cell destruction is quite variable, being rapid in some individuals (mainly infants and children) and slow in others (mainly adults). Some patients, particularly children and adolescents, may present with ketoacidosis as the first manifestation of the disease. Others have modest fasting hyperglycemia that can rapidly change to severe hyperglycemia and/or ketoacidosis in the presence of infection or other

stress. Still others, particularly adults, may retain residual β-cell function sufficient to prevent ketoacidosis for many years; such individuals eventually become dependent on insulin for survival and are at risk for ketoacidosis. At this latter stage of the disease, there is little or no insulin secretion, as manifested by low or undetectable levels of plasma C-peptide. Immune-mediated diabetes commonly occurs in childhood and adolescence, but it can occur at any age, even in the 8th and 9th decades of life.

Idiopathic diabetes

Some forms of type 1 diabetes have no known etiologies. Some of these patients have permanent insulinopenia and are prone to ketoacidosis, but have no evidence of autoimmunity. Although only a minority of patients with type 1 diabetes fall into this category, of those who do, most are of African or Asian ancestry. Individuals with this form of diabetes suffer from episodic ketoacidosis and exhibit varying degrees of insulin deficiency between episodes. This form of diabetes is strongly inherited, lacks immunological evidence for β-cell autoimmunity, and is not HLA associated. An absolute requirement for insulin replacement therapy in affected patients may come and go.[33]

Type 2:

This form of diabetes, which accounts for ~90–95% of those with diabetes, previously referred to as non-insulin-dependent diabetes, type 2 diabetes, or adult-onset diabetes, encompasses individuals who have insulin resistance and usually have relative (rather than absolute) insulin deficiency at least initially, and often throughout their lifetime, these individuals do not need insulin treatment to survive. There are probably many different causes of this form of diabetes. Although the specific etiologies are not known, autoimmune destruction of β-cells does not occur, and patients do not have any of the other causes of diabetes listed.

Most patients with this form of diabetes are obese, and obesity itself causes some degree of insulin resistance. Patients who are not obese by traditional weight criteria may have an increased percentage of body fat distributed predominantly in the abdominal region.[34] Despite having lower prevalence of obesity as defined by body mass index (BMI), Asian Indians tend to have greater waist circumference and waist to hip ratios thus having a greater degree of central obesity. Again, Asian Indians have more total abdominal and visceral fat. For any given BMI43 and for any given body fat they have increased insulin resistance. Moreover, they have lower levels of the protective adipokine, adiponectin and have increased levels of adipose tissue metabolites. Studies on neonates suggested that Indian babies are born smaller but relatively fatter compared to Caucasian babies and are referred to as "the thin fat Indian baby". A recent study confirmed this finding and suggested that the "thin fat phenotype" in neonates persisted in childhood and could be a forerunner of the diabetogenic adult phenotype. These findings suggest that Asian Indians are more prone to diabetes and related metabolic abnormalities.[26]

The disease occurs more frequently in women with prior GDM (Gestational Diabetes Mellitus) and in individuals with hypertension or dyslipidemia, and its frequency varies in different racial/ethnic subgroups. It is often associated with a strong genetic predisposition, more so than is the autoimmune form of type 1diabetes. However, the genetics of this form of diabetes are complex and not clearly defined.[26]

Several studies on migrant Indians across the globe have shown that Asian Indians have an increased risk for developing type 2 diabetes and related metabolic abnormalities compared to other ethnic groups.[35,36,37,38]

Although the exact reasons are still not clear, certain unique clinical and biochemical characteristics of this ethnic group collectively called as the "Asian Indian phenotype" is considered to be one of the major factors contributing to the increased predilection towards diabetes Epidemiology of type 2 diabetes: Indian scenario.[26]

Impaired insulin secretion is found uniformly in type 2 diabetic patients in all ethnic populations. The β-cells are unable to read the severity of insulin resistance and fail to adjust their secretion of insulin to maintain normal glucose tolerance. In these patients, the fasting plasma insulin concentration is normal or increased and basal insulin secretion is elevated. Gluco-toxicity, lipo-toxicity are among the acquired defects that can lead to impaired insulin secretion. Recently, deficiency of or resistance to "incretins" have been implicated in the pathogenesis of β-cell dysfunction in type -2 diabetic patients.[2]

Amylin also known as IAPP (islet amyloid polypeptide) has been implicated in progressive β-cells failure in type–2 diabetes mellitus. IAPP, which is packaged with insulin in secretary granules and co-secreted into the sinusoidal space, is the precursor for the amyloid deposits that are frequently observed in type – 2 diabetics. Following its secretion, amylin accumulates extracellularly in close proximity to the β-cells and it has been suggested that amylin deposits cause β-cell dysfunction. However this theory is not very well accepted, due to failure of inhibitory effect of amylin on insulin secretion when the peptide was infused in pharmacologic doses in rats, rabbits and humans.

The number of β-cells within the pancreas is an important determinant of the amount of insulin that is secreted. Most but not all studies have demonstrated a modest reduction (20%-40%) in β-cells mass. Low birth weight is associated with the development of IGT and type -2 diabetes in a number of populations. Developmental studies in animals and humans

have demonstrated that poor nutrition impair insulin secretion or reduce β-cell mass.

The cross sectional studies and long term, prospective longitudinal studies have shown hyper insulinemia to precede the onset of type -2 diabetes in all ethnic populations with high incidence of type 2 diabetes Himsworth and Kerr in 1939 were the first to demonstrate that the tissue sensitivity to insulin is diminished in type 2 diabetic patients.[2]

De Fronzo et al using the more physiological euglycemic insulin clamp technique, have provided the most conclusive documentation that insulin resistance is characteristic feature of lean, as well as that of obese, type 2 diabetic individuals. The combined effects of insulin and hyperglycemia to promote glucose disposal are dependent on three tightly coupled mechanisms.

- Suppression of endogenous (primarily hepatic) production
- Stimulation of glucose uptake by the splanchnic tissue.(hepatic plus gastrointestinal)
- Stimulation of glucose uptake by peripheral tissues, primarily muscle.

In type 2 diabetes, the cause is a combination of resistance to insulin action and an inadequate compensatory insulin secretary response. In the latter category, a degree of hyperglycemia sufficient to cause pathologic and functional changes in various target tissues, but without clinical symptoms, may be present for a long period of time before diabetes is detected. During this asymptomatic period, it is possible to demonstrate an abnormality in carbohydrate metabolism by measurement of plasma glucose in the fasting state or after a challenge with an oral glucose load.[33]

Risk factors for the development of type-2 diabetes

- Age greater than 45 years
- Diabetes during a previous pregnancy

- Excess body weight (especially around the waist)
- Family history of diabetes
- Given birth to a baby weighing more than 9 pounds
- HDL cholesterol under 35 mg/dL
- High blood levels of triglycerides, a type of fat molecule (250 mg/dL or more)
- High blood pressure (greater than or equal to 140/90 mmHg)
- Impaired glucose tolerance
- Low activity level (exercising less than 3 times a week)
- Metabolic syndrome
- Polycystic ovarian syndrome
- A condition called acanthosis nigricans, which causes dark, thickened skin around the neck or armpits

Persons from certain ethnic groups, including African Americans, Hispanic Americans, Asian Americans, and Native Americans, have a higher risk for diabetes.[39]

Other specific types of diabetes

Genetic defects of the β-cell.

Several forms of diabetes are associated with monogenetic defects in β-cell function. These forms of diabetes are frequently characterized by onset of hyperglycemia at an early age (generally before age 25 years). They are referred to as maturity-onset diabetes of the young (MODY) and are characterized by impaired insulin secretion with minimal or no defects in insulin action. They are inherited in an autosomal dominant pattern. Abnormalities at six genetic loci on different chromosomes have been identified to date. The most common form is associated with mutations on chromosome 12 in a hepatic

transcription factor referred to as hepatocyte nuclear factor (HNF)-1α. A second form is associated with mutations in the glucokinase gene on chromosome 7p and results in a defective glucokinase molecule. Glucokinase converts glucose to glucose-6-phosphate, the metabolism of which, in turn, stimulates insulin secretion by the β-cell. Thus, glucokinase serves as the "glucose sensor" for the β-cell. Because of defects in the glucokinase gene, increased plasma levels of glucose are necessary to elicit normal levels of insulin secretion. The less common forms result from mutations in other transcription factors, including HNF-4α, HNF-1β, insulin promoter factor (IPF)-1, and NeuroD1.[40]

Point mutations in mitochondrial DNA have been found to be associated with diabetes and deafness. The most common mutation occurs at position 3,243 in the tRNA leucine gene, leading to an A-to-G transition. An identical lesion occurs in the MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like syndrome); however, diabetes is not part of this syndrome, suggesting different phenotypic expressions of this genetic lesion.

Genetic abnormalities that result in the inability to convert proinsulin to insulin have been identified in a few families, and such traits are inherited in an autosomal dominant pattern. The resultant glucose intolerance is mild. Similarly, the production of mutant insulin molecules with resultant impaired receptor binding has also been identified in a few families and is associated with an autosomal inheritance and only mildly impaired or even normal Glucose.

Genetic defects in insulin action

There are unusual causes of diabetes that result from genetically determined abnormalities of insulin action. The metabolic abnormalities associated with mutations of

the insulin receptor may range from hyperinsulinemia and modest hyperglycemia to severe diabetes. Some individuals with these mutations may have acanthosis nigricans. Women may be virilized and have enlarged, cystic ovaries. In the past, this syndrome was termed type A insulin resistance. Leprechaunism and the Rabson-Mendenhall syndrome are two pediatric syndromes that have mutations in the insulin receptor gene with subsequent alterations in insulin receptor function and extreme insulin resistance. The former has characteristic facial features and is usually fatal in infancy, while the latter is associated with abnormalities of teeth and nails and pineal gland hyperplasia.

Alterations in the structure and function of the insulin receptor cannot be demonstrated in patients with insulin-resistant lipoatrophic diabetes. Therefore, it is assumed that the lesion(s) must reside in the postreceptor signal transduction pathways.[40]

Diseases of the exocrine pancreas

Any process that diffusely injures the pancreas can cause diabetes. Acquired processes include pancreatitis, trauma, infection, pancreatectomy, and pancreatic carcinoma. With the exception of that caused by cancer, damage to the pancreas must be extensive for diabetes to occur; adrenocarcinomas that involve only a small portion of the pancreas have been associated with diabetes. This implies a mechanism other than simple reduction in β-cell mass. If extensive enough, cystic fibrosis and hemochromatosis will also damage β-cells and impair insulin secretion. Fibrocalculous pancreatopathy may be accompanied by abdominal pain radiating to the back and pancreatic calcifications identified on X-ray examination. Pancreatic fibrosis and calcium stones in the exocrine ducts have been found at autopsy.[40]

Endocrinopathies

Several hormones (e.g., growth hormone, cortisol, glucagon, epinephrine) antagonize insulin action. Excess amounts of these hormones (e.g., acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, respectively) can cause diabetes. This generally occurs in individuals with preexisting defects in insulin secretion, and hyperglycemia typically resolves when the hormone excess is resolved.

Somatostatinoma- and aldosteronoma-induced hypokalemia can cause diabetes, at least in part, by inhibiting insulin secretion. Hyperglycemia generally resolves after successful removal of the tumor.[40]

Drug- or chemical-induced diabetes

Many drugs can impair insulin secretion. These drugs may not cause diabetes by themselves, but they may precipitate diabetes in individuals with insulin resistance. In such cases, the classification is unclear because the sequence or relative importance of β-cell dysfunction and insulin resistance is unknown. Certain toxins such as Vacor (a rat poison) and intravenous pentamidine can permanently destroy pancreatic β-cells. Such drug reactions fortunately are rare. There are also many drugs and hormones that can impair insulin action. Examples include nicotinic acid and glucocorticoids. Patients receiving α-interferon have been reported to develop diabetes associated with islet cell antibodies and, in certain instances, severe insulin deficiency. The list shown in following table reflects the more commonly recognized drug-, hormone-, or toxin-induced forms of diabetes.

Table 1 : Etiologic classification of diabetes mellitus

I. Type 1 diabetes (β-cell destruction, usually leading to absolute insulin deficiency)

   1. Immune mediated

2. Idiopathic

II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)

III. Other specific types

1. Genetic defects of β-cell function
    a. Chromosome 12, HNF-1α (MODY3)
    b. Chromosome 7, glucokinase (MODY2)
    c. Chromosome 20, HNF-4α (MODY1)
    d. Chromosome 13, insulin promoter factor-1 (IPF-1; MODY4)
    e. Chromosome 17, HNF-1β (MODY5)
    f. Chromosome 2, *NeuroD1* (MODY6)
    g. Mitochondrial DNA
    h. Others
2. Genetic defects in insulin action
    a. Type A insulin resistance
    b. Leprechaunism
    c. Rabson-Mendenhall syndrome
    d. Lipoatrophic diabetes
    e. Others
3. Diseases of the exocrine pancreas
    a. Pancreatitis
    b. Trauma/pancreatectomy
    c. Neoplasia

d. Cystic fibrosis

e. Hemochromatosis

f. Fibrocalculous pancreatopathy

g. Others

4. Endocrinopathies

a. Acromegaly

b. Cushing's syndrome

c. Glucagonoma

d. Pheochromocytoma

e. Hyperthyroidism

f. Somatostatinoma

g. Aldosteronoma

h. Others

5. Drug or chemical induced

a. Vacor

b. Pentamidine

c. Nicotinic acid

d. Glucocorticoids

e. Thyroid hormone

f. Diazoxide

g. β-adrenergic agonists

h. Thiazides

i. Dilantin

j. γ-Interferon

k. Others

6. Infections

a. Congenital rubella

b. Cytomegalovirus

c. Others

7. Uncommon forms of immune-mediated diabetes

a. "Stiff-man" syndrome

b. Anti-insulin receptor antibodies

c. Others

8. Other genetic syndromes sometimes associated with diabetes

a. Down syndrome

b. Klinefelter syndrome

c. Turner syndrome

d. Wolfram syndrome

e. Friedreich ataxia

f. Huntington chorea

g. Laurence-Moon-Biedl syndrome

h. Myotonic dystrophy

i. Porphyria

j. Prader-Willi syndrome

k. Others

IV. Gestational diabetes mellitus

Infections

Certain viruses have been associated with β-cell destruction. Diabetes occurs in patients with congenital rubella, although most of these patients have HLA and immune markers characteristic of type 1 diabetes. In addition, coxsackievirus B, cytomegalovirus, adenovirus, and mumps have been implicated in inducing certain cases of the disease.

Uncommon forms of immune-mediated diabetes

In this category, there are two known conditions, and others are likely to occur. The stiff-man syndrome is an autoimmune disorder of the central nervous system characterized by stiffness of the axial muscles with painful spasms. Patients usually have high titers of the GAD autoantibodies, and approximately one-third will develop diabetes.

Anti-insulin receptor antibodies can cause diabetes by binding to the insulin receptor, thereby blocking the binding of insulin to its receptor in target tissues. However, in some cases, these antibodies can act as an insulin agonist after binding to the receptor and can thereby cause hypoglycemia. Anti-insulin receptor antibodies are occasionally found in patients with systemic lupus erythematosus and other autoimmune diseases. As in other states of extreme insulin resistance, patients with anti-insulin receptor antibodies often have acanthosis nigricans. In the past, this syndrome was termed type B insulin resistance.

Other genetic syndromes sometimes associated with diabetes

Many genetic syndromes are accompanied by an increased incidence of diabetes. These include the chromosomal abnormalities of Down syndrome, Klinefelter syndrome, and Turner syndrome. Wolfram's syndrome is an autosomal recessive disorder characterized by insulin-deficient diabetes and the absence of β-cells at autopsy. Additional manifestations include diabetes insipidus, hypogonadism, optic atrophy, and neural deafness.

Gestational diabetes mellitus

For many years, GDM has been defined as any degree of glucose intolerance with onset or first recognition during pregnancy. Although most cases resolve with delivery, the definition applied whether or not the condition persisted after pregnancy and did not exclude the possibility that unrecognized glucose intolerance may have antedated or begun concomitantly with the pregnancy. This definition facilitated a uniform strategy for detection and classification of GDM, but its limitations were recognized for many years. As the ongoing epidemic of obesity and diabetes has led to more type 2 diabetes in women of childbearing age, the number of pregnant women with undiagnosed type 2 diabetes has increased.[40]

SYMPTOMS OF DIABETES

Symptoms of diabetes

The following are the most common symptoms of hyperglycemia (high blood sugar). However, each individual may experience symptoms differently. Symptoms may include:

- rapid weight loss
- feeling sick
- thirst
- vomiting
- fatigue
- blurred vision
- fainting
- hunger
- fatigue

- shakiness
- headaches
- confusion
- dizziness
- sudden moodiness or behavior changes
- sweating [6]

Acute, life-threatening consequences of uncontrolled diabetes are hyperglycemia with ketoacidosis or the nonketotic hyperosmolar syndrome. Ketoacidosis seldom occurs spontaneously in this type of diabetes; when seen, it usually arises in association with the stress of another illness such as infection. This form of diabetes frequently goes undiagnosed for many years because the hyperglycemia develops gradually and at earlier stages is often not severe enough for the patient to notice any of the classic symptoms of diabetes. Nevertheless, such patients are at increased risk of developing macrovascular and microvascular complications. Whereas patients with this form of diabetes may have insulin levels that appear normal or elevated, the higher blood glucose levels in these diabetic patients would be expected to result in even higher insulin values had their β-cell function been normal. Thus, insulin secretion is defective in these patients and insufficient to compensate for insulin resistance. Insulin resistance may improve with weight reduction and/or pharmacological treatment of hyperglycemia but is seldom restored to normal. The risk of developing this form of diabetes increases with age, obesity, and lack of physical activity.

A degree of hyperglycemia sufficient to cause pathologic and functional changes in various target tissues, but without clinical symptoms, may be present for a long period of

time before diabetes is detected. During this asymptomatic period, it is possible to demonstrate an abnormality in carbohydrate metabolism by measurement of plasma glucose in the fasting state or after a challenge with an oral glucose load.

Complications

Long-term complications of diabetes leads to additional complications which include micro vascular, macro vascular and neuropathic diseases. The micro vascular abnormalities are proliferative scarring of retina (diabetic retinopathy), with potential loss of vision and renal disease (diabetic nephropathy) leading to renal failure. peripheral neuropathy with risk of foot ulcers, amputations, and Charcot joints; and autonomic neuropathy causing gastrointestinal, genitourinary, and cardiovascular symptoms and sexual dysfunction. The macro vascular abnormalities are due to accelerated atherosclerosis which results in increased incidence of stroke and myocardial infarction. The neuropathic abnormalities (diabetic neuropathy) involve the autoimmune nervous system and peripheral nerves. Hypertension and abnormalities of lipoprotein metabolism are often found in people with diabetes.[2]

The degree of hyperglycemia (if any) may change over time, depending on the extent of the underlying disease process. A disease process may be present but may not have progressed far enough to cause hyperglycemia. The same disease process can cause impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) without fulfilling the criteria for the diagnosis of diabetes. In some individuals with diabetes, adequate glycemic control can be achieved with weight reduction, exercise, and/or oral glucose-lowering agents. These individuals therefore do not require insulin. Other individuals who have some residual insulin secretion but require exogenous insulin for adequate glycemic

control can survive without it. Individuals with extensive β-cell destruction and therefore no residual insulin secretion require insulin for survival. The severity of the metabolic abnormality can progress, regress, or stay the same. Thus, the degree of hyperglycemia reflects the severity of the underlying metabolic process and its treatment more than the nature of the process itself.

Position Statement chart

Assigning a type of diabetes to an individual often depends on the circumstances present at the time of diagnosis, and many diabetic individuals do not easily fit into a single class. For example, a person with gestational diabetes mellitus (GDM) may continue to be hyperglycemic after delivery and may be determined to have, in fact, type 2 diabetes. Alternatively, a person who acquires diabetes because of large doses of exogenous steroids may become normoglycemic once the glucocorticoids are discontinued, but then may develop diabetes many years later after recurrent episodes of pancreatitis. Another example would be a person treated with thiazides who develops diabetes years later. Because thiazides in themselves seldom cause severe hyperglycemia, such individuals probably have type 2 diabetes that is exacerbated by the drug. Thus, for the clinician and patient, it is less important to label the particular type of diabetes than it is to understand the pathogenesis of the hyperglycemia and to treat it effectively.

CATEGORIES OF INCREASED RISK FOR DIABETES

In 1997 and 2003, The Expert Committee on Diagnosis and Classification of Diabetes Mellitus recognized an intermediate group of individuals whose glucose levels do not meet criteria for diabetes, yet are higher than those considered normal. These people were defined as having impaired fasting glucose (IFG) [fasting plasma glucose (FPG) levels

100 mg/dl (5.6 mmol/l) to 125 mg/dl (6.9 mmol/l)], or impaired glucose tolerance (IGT) [2-h values in the oral glucose tolerance test (OGTT) of 140 mg/dl (7.8 mmol/l) to 199 mg/dl (11.0 mmol/l)].

Individuals with IFG and/or IGT have been referred to as having pre-diabetes, indicating the relatively high risk for the future development of diabetes. IFG and IGT should not be viewed as clinical entities in their own right but rather risk factors for diabetes as well as cardiovascular disease. They can be observed as intermediate stages in any of the disease processes listed earlier. IFG and IGT are associated with obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension. Structured lifestyle intervention, aimed at increasing physical activity and producing 5–10% loss of body weight, and certain pharmacological agents have been demonstrated to prevent or delay the development of diabetes in people with IGT; the potential impact of such interventions to reduce mortality or the incidence of cardiovascular disease has not been demonstrated to date. It should be noted that the 2003 ADA Expert Committee report reduced the lower FPG cut point to define IFG from 110 mg/dl (6.1 mmol/l) to 100 mg/dl (5.6 mmol/l), in part to ensure that prevalence of IFG was similar to that of IGT. However, the World Health Organization (WHO) and many other diabetes organizations did not adopt this change in the definition of IFG.[41]

As A1C is used more commonly to diagnose diabetes in individuals with risk factors, it will also identify those at higher risk for developing diabetes in the future. When recommending the use of the A1C to diagnose diabetes in its 2009 report, the International Expert Committee stressed the continuum of risk for diabetes with all glycemic measures and did not formally identify an equivalent intermediate category for A1C. The group did

note that those with A1C levels above the laboratory "normal" range but below the diagnostic cut point for diabetes (6.0 to <6.5%) are at very high risk of developing diabetes. Indeed, incidence of diabetes in people with A1C levels in this range is more than 10 times that of people with lower levels. However, the 6.0 to <6.5% range fails to identify a substantial number of patients who have IFG and/or IGT. Prospective studies indicate that people within the A1C range of 5.5–6.0% have a 5-year cumulative incidence of diabetes that ranges from 12 to 25% , which is appreciably (three- to eightfold) higher than incidence in the U.S. population as a whole . Analyses of nationally representative data from the National Health and Nutrition Examination Survey (NHANES) indicate that the A1C value that most accurately identifies people with IFG or IGT falls between 5.5 and 6.0%. In addition, linear regression analyses of these data indicate that among the nondiabetic adult population, an FPG of 110 mg/dl (6.1 mmol/l) corresponds to an A1C of 5.6%, while an FPG of 100 mg/dl (5.6 mmol/l) corresponds to an A1C of 5.4% (R.T. Ackerman, personal communication). Finally, evidence from the Diabetes Prevention Program (DPP), wherein the mean A1C was 5.9% (SD 0.5%), indicates that preventive interventions are effective in groups of people with A1C levels both below and above 5.9%. For these reasons, the most appropriate A1C level above which to initiate preventive interventions is likely to be somewhere in the range of 5.5–6%.[41]

As was the case with FPG and 2-h PG, defining a lower limit of an intermediate category of A1C is somewhat arbitrary, as the risk of diabetes with any measure or surrogate of glycemia is a continuum, extending well into the normal ranges. To maximize equity and efficiency of preventive interventions, such an A1C cut point should balance the costs of "false negatives" (failing to identify those who are going to develop diabetes) against the

costs of "false positives" (falsely identifying and then spending intervention resources on those who were not going to develop diabetes anyway).[41]

Compared to the fasting glucose cut point of 100 mg/dl (5.6 mmol/l), an A1C cut point of 5.7% is less sensitive but more specific and has a higher positive predictive value to identify people at risk for later development of diabetes. A large prospective study found that a 5.7% cut point has a sensitivity of 66% and specificity of 88% for the identification of subsequent 6-year diabetes incidence. Receiver operating curve analyses of nationally representative U.S. data (NHANES 1999-2006) indicate that an A1C value of 5.7% has modest sensitivity (39-45%) but high specificity (81-91%) to identify cases of IFP (FPG >100 mg/dl) (5.6 mmol/l) or IGT (2-h glucose > 140 mg/dl) (R.T. Ackerman, personal communication). Other analysts suggest that an A1C of 5.7% is associated with diabetes risk similar to the high-risk participants in the DPP (R.T. Ackerman, personal communication). Hence, it is reasonable to consider an A1C range of 5.7 to 6.4% as identifying individuals with high risk for future diabetes and to whom the term pre-diabetes may be applied if desired.[41]

Individuals with an A1C of 5.7–6.4% should be informed of their increased risk for diabetes as well as cardiovascular disease and counseled about effective strategies, such as weight loss and physical activity, to lower their risks. As with glucose measurements, the continuum of risk is curvilinear, so that as A1C rises, the risk of diabetes rises disproportionately. Accordingly, interventions should be most intensive and follow-up should be particularly vigilant for those with A1C levels above 6.0%, who should be considered to be at very high risk. However, just as an individual with a fasting glucose of 98 mg/dl (5.4 mmol/l) may not be at negligible risk for diabetes, individuals with A1C levels

below 5.7% may still be at risk, depending on level of A1C and presence of other risk factors, such as obesity and family history.[41]

Following table summarizes the categories of increased risk for diabetes. Evaluation of patients at risk should incorporate a global risk factor assessment for both diabetes and cardiovascular disease. Screening for and counseling about risk of diabetes should always be in the pragmatic context of the patient's co morbidities, life expectancy, personal capacity to engage in lifestyle change, and overall health goals.

Table : Criteria for the diagnosis of diabetes

1. A1C ≥6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.

   OR

2. FPG ≥126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.

   OR

3. Two-hour plasma glucose ≥200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

   OR

4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dl (11.1 mmol/l).

In the absence of unequivocal hyperglycemia, criteria 1–3 should be confirmed by repeat testing.

DIAGNOSTIC CRITERIA FOR DIABETES MELLITUS

For decades, the diagnosis of diabetes has been based on glucose criteria, either the FPG or the 75-g OGTT. In 1997, the first Expert Committee on the Diagnosis and Classification of Diabetes Mellitus revised the diagnostic criteria, using the observed association between FPG levels and presence of retinopathy as the key factor with which to identify threshold glucose level. The Committee examined data from three cross-sectional epidemiologic studies that assessed retinopathy with fundus photography or direct ophthalmoscopy and measured glycemia as FPG, 2-h PG, and A1C. These studies demonstrated glycemic levels below which there was little prevalent retinopathy and above which the prevalence of retinopathy increased in an apparently linear fashion. The deciles of the three measures at which retinopathy began to increase were the same for each measure within each population. Moreover, the glycemic values above which retinopathy increased were similar among the populations. These analyses helped to inform a new diagnostic cut point of ≥126 mg/dl (7.0 mmol/l) for FPG and confirmed the long-standing diagnostic 2-h PG value of ≥200 mg/dl (11.1 mmol/l).[41]

A1C is a widely used marker of chronic glycemia, reflecting average blood glucose levels over a 2- to 3-month period of time. The test plays a critical role in the management of the patient with diabetes, since it correlates well with both microvascular and, to a lesser extent, macrovascular complications and is widely used as the standard biomarker for the adequacy of glycemic management. Prior Expert Committees have not recommended use of the A1C for diagnosis of diabetes, in part due to lack of standardization of the assay. However, A1C assays are now highly standardized so that their results can be uniformly applied both temporally and across populations. In their recent report, an International

Expert Committee, after an extensive review of both established and emerging epidemiological evidence, recommended the use of the A1C test to diagnose diabetes, with a threshold of ≥6.5%, and ADA affirms this decision. The diagnostic A1C cut point of 6.5% is associated with an inflection point for retinopathy prevalence, as are the diagnostic thresholds for FPG and 2-h PG. The diagnostic test should be performed using a method that is certified by the National Glycohemoglobin Standardization Program (NGSP) and standardized or traceable to the Diabetes Control and Complications Trial reference assay. Point-of-care A1C assays are not sufficiently accurate at this time to use for diagnostic purposes.[41]

There is an inherent logic to using a more chronic versus an acute marker of dysglycemia, particularly since the A1C is already widely familiar to clinicians as a marker of glycemic control. Moreover, the A1C has several advantages to the FPG, including greater convenience, since fasting is not required, evidence to suggest greater preanalytical stability, and less day-to-day perturbations during periods of stress and illness. These advantages, however, must be balanced by greater cost, the limited availability of A1C testing in certain regions of the developing world, and the incomplete correlation between A1C and average glucose in certain individuals. In addition, the A1C can be misleading in patients with certain forms of anemia and hemoglobinopathies, which may also have unique ethnic or geographic distributions. For patients with a hemoglobinopathy but normal red cell turnover, such as sickle cell trait, an A1C assay without interference from abnormal hemoglobins should be used. For conditions with abnormal red cell turnover, such as anemias from hemolysis and iron deficiency, the diagnosis of diabetes must employ glucose criteria exclusively.[41]

The established glucose criteria for the diagnosis of diabetes remain valid. These include the FPG and 2-h PG. Additionally, patients with severe hyperglycemia such as those who present with severe classic hyperglycemic symptoms or hyperglycemic crisis can continue to be diagnosed when a random (or casual) plasma glucose of ≥200 mg/dl (11.1 mmol/l) is found. It is likely that in such cases the health care professional would also measure an A1C test as part of the initial assessment of the severity of the diabetes and that it would (in most cases) be above the diagnostic cut point for diabetes. However, in rapidly evolving diabetes, such as the development of type 1 diabetes in some children, A1C may not be significantly elevated despite frank diabetes.[41]

Just as there is less than 100% concordance between the FPG and 2-h PG tests, there is not full concordance between A1C and either glucose-based test. Analyses of NHANES data indicate that, assuming universal screening of the undiagnosed, the A1C cut point of ≥6.5% identifies one-third fewer cases of undiagnosed diabetes than a fasting glucose cut point of ≥126 mg/dl (7.0 mmol/l) (cdc website tbd). However, in practice, a large portion of the population with type 2 diabetes remains unaware of their condition. Thus, it is conceivable that the lower sensitivity of A1C at the designated cut point will be offset by the test's greater practicality, and that wider application of a more convenient test (A1C) may actually increase the number of diagnoses made.

Further research is needed to better characterize those patients whose glycemic status might be categorized differently by two different tests (e.g., FPG and A1C), obtained in close temporal approximation. Such discordance may arise from measurement variability, change over time, or because A1C, FPG, and postchallenge glucose each measure different physiological processes. In the setting of an elevated A1C but “nondiabetic” FPG, the

likelihood of greater postprandial glucose levels or increased glycation rates for a given degree of hyperglycemia may be present. In the opposite scenario (high FPG yet A1C below the diabetes cut point), augmented hepatic glucose production or reduced glycation rates may be present.[41]

As with most diagnostic tests, a test result diagnostic of diabetes should be repeated to rule out laboratory error, unless the diagnosis is clear on clinical grounds, such as a patient with classic symptoms of hyperglycemia or hyperglycemic crisis. It is preferable that the same test be repeated for confirmation, since there will be a greater likelihood of concurrence in this case. For example, if the A1C is 7.0% and a repeat result is 6.8%, the diagnosis of diabetes is confirmed. However, there are scenarios in which results of two different tests (e.g., FPG and A1C) are available for the same patient. In this situation, if the two different tests are both above the diagnostic thresholds, the diagnosis of diabetes is confirmed.[41]

On the other hand, when two different tests are available in an individual and the results are discordant, the test whose result is above the diagnostic cut point should be repeated, and the diagnosis is made on the basis of the confirmed test. That is, if a patient meets the diabetes criterion of the A1C (two results ≥6.5%) but not the FPG (<126 mg/dl or 7.0 mmol/l), or vice versa, that person should be considered to have diabetes. Admittedly, in most circumstance the "nondiabetic" test is likely to be in a range very close to the threshold that defines diabetes.[41]

Since there is preanalytic and analytic variability of all the tests, it is also possible that when a test whose result was above the diagnostic threshold is repeated, the second value will be below the diagnostic cut point. This is least likely for A1C, somewhat more

likely for FPG, and most likely for the 2-h PG. Barring a laboratory error, such patients are likely to have test results near the margins of the threshold for a diagnosis. The healthcare professional might opt to follow the patient closely and repeat the testing in 3–6 months.

The decision about which test to use to assess a specific patient for diabetes should be at the discretion of the health care professional, taking into account the availability and practicality of testing an individual patient or groups of patients. Perhaps more important than which diagnostic test is used, is that the testing for diabetes be performed when indicated. There is discouraging evidence indicating that many at-risk patients still do not receive adequate testing and counseling for this increasingly common disease, or for its frequently accompanying cardiovascular risk factors. The current diagnostic criteria for diabetes are summarized below.[41]

Following table is suggestive of increased risk for diabetes

FPG 100–125 mg/dl (5.6–6.9 mmol/l) [IFG]

2-h PG on the 75-g OGTT 140–199 mg/dl (7.8–11.0 mmol/l) [IGT]

A1C 5.7–6.4%

- For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at higher ends of the range.

Diagnosis of GDM

The criteria for abnormal glucose tolerance in pregnancy are those of Carpenter and Coustan. Recommendations from ADA's Fourth International Workshop-Conference on Gestational Diabetes Mellitus held in March 1997 support the use of the Carpenter/Coustan diagnostic criteria as well as the alternative use of a diagnostic 75-g 2-h OGTT. These criteria are summarized below.

Testing for gestational diabetes

Previous recommendations included screening for GDM performed in all pregnancies. However, there are certain factors that place women at lower risk for the development of glucose intolerance during pregnancy, and it is likely not cost-effective to screen such patients. Pregnant women who fulfill *all* of these criteria need not be screened for GDM. This low-risk group comprises women who:

- are <25 years of age
- are a normal body weight
- have no family history (i.e., first-degree relative) of diabetes
- have no history of abnormal glucose metabolism
- have no history of poor obstetric outcome
- are not members of an ethnic/racial group with a high prevalence of diabetes (e.g., Hispanic American, Native American, Asian American, African American, Pacific Islander)

Risk assessment for GDM should be undertaken at the first prenatal visit. Women with clinical characteristics consistent with a high risk of GDM (marked obesity, personal history of GDM, glycosuria, or a strong family history of diabetes) should undergo glucose testing (see below) as soon as feasible. If they are found not to have GDM at that initial screening, they should be retested between 24 and 28 weeks of gestation. Women of average risk should have testing undertaken at 24–28 weeks of gestation.

An FPG level >126 mg/dl (7.0 mmol/l) or a casual plasma glucose >200 mg/dl (11.1 mmol/l) meets the threshold for the diagnosis of diabetes. In the absence of unequivocal hyperglycemia, the diagnosis must be confirmed on a subsequent day. Confirmation of the

diagnosis precludes the need for any glucose challenge. In the absence of this degree of hyperglycemia, evaluation for GDM in women with average or high-risk characteristics should follow one of two approaches.

One-step approach

Perform a diagnostic OGTT without prior plasma or serum glucose screening. The one-step approach may be cost-effective in high-risk patients or populations (e.g., some Native-American groups).

Two-step approach

Perform an initial screening by measuring the plasma or serum glucose concentration 1 h after a 50-g oral glucose load (glucose challenge test [GCT]) and perform a diagnostic OGTT on that subset of women exceeding the glucose threshold value on the GCT. When the two-step approach is used, a glucose threshold value >140 mg/dl (7.8 mmol/l) identifies ~80% of women with GDM, and the yield is further increased to 90% by using a cutoff of >130 mg/dl (7.2 mmol/l).

With either approach, the diagnosis of GDM is based on an OGTT. Diagnostic criteria for the 100-g OGTT are derived from the original work of O'Sullivan and Mahan. Modified by Carpenter and Coustan and are shown below. Alternatively, the diagnosis can be made using a 75-g glucose load and the glucose threshold values listed for fasting, 1 h, and 2 h bottom, however, this test is not as well validated as the 100-g OGTT.[41]

TESTING FOR DIABETES IN ASYMPTOMATIC PATIENTS

Recommendations

- Testing to detect type 2 diabetes and assess risk for future diabetes in asymptomatic people should be considered in adults of any age who are overweight or obese (BMI ≥25

kg/m^2) and who have one or more additional risk factors for diabetes. In those without these risk factors, testing should begin at age 45 years.

- If tests are normal, repeat testing should be carried out at least at 3-year intervals.
- To test for diabetes or to assess risk of future diabetes, either A1C, FPG, or 2-h 75-g OGTT are appropriate.
- In those identified with increased risk for future diabetes, identify and, if appropriate, treat other CVD risk factors.

Criteria for testing for diabetes in asymptomatic adult individuals

1. Testing should be considered in all adults who are overweight (BMI ≥25 kg/m^2) and have additional risk factors:
    - physical inactivity
    - first-degree relative with diabetes
    - members of a high-risk ethnic population (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
    - women who delivered a baby weighing >9 lb or were diagnosed with GDM
    - hypertension (≥140/90 mmHg or on therapy for hypertension)
    - HDL cholesterol level <35 mg/dl (0.90 mmol/l) and/or a triglyceride level >250 mg/dl (2.82 mmol/l)
    - women with polycystic ovary syndrome
    - A1C ≥5.7%, IGT, or IFG on previous testing
    - other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
    - history of CVD

2. In the absence of the above criteria, testing diabetes should begin at age 45 years
3. If results are normal, testing should be repeated at least at 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.

At-risk BMI may be lower in some ethnic groups.

- For many illnesses there is a major distinction between screening and diagnostic testing. However, for diabetes the same tests would be used for "screening" as for diagnosis. Type 2 diabetes has a long asymptomatic phase and significant clinical risk markers. Diabetes may be identified anywhere along a spectrum of clinical scenarios ranging from a seemingly low-risk individual who happens to have glucose testing, to a higher-risk individual who the provider tests because of high suspicion of diabetes, to the symptomatic patient. The discussion here in is primarily framed as testing for diabetes in individuals without symptoms. Testing for diabetes will also detect individuals at increased future risk for diabetes, here in referred to as pre-diabetic.

A. Testing for type 2 diabetes and risk of future diabetes in adults

Type 2 diabetes is frequently not diagnosed until complications appear, and approximately one-fourth of all people with diabetes in the U.S. may be undiagnosed. Although the effectiveness of early identification of pre-diabetes and diabetes through mass testing of asymptomatic individuals has not been proven definitively (and rigorous trials to provide such proof are unlikely to occur), pre-diabetes and diabetes meet established criteria for conditions in which early detection is appropriate. Both conditions are common, are increasing in prevalence, and impose significant public health burdens. There is a long presymptomatic phase before the diagnosis of type 2 diabetes is usually made. Relatively simple tests are available to detect preclinical disease.[42]

Additionally, the duration of glycemic burden is a strong predictor of adverse outcomes, and effective interventions exist to prevent progression of pre-diabetes to diabetes. Following are the recommendations for testing for diabetes in asymptomatic undiagnosed adults .Testing should be considered in adults of any age with BMI ≥25 kg/m^2 and one or more risk factors for diabetes. Because age is a major risk factor for diabetes, testing of those without other risk factors should begin no later than at age 45 years.

- The appropriate interval between tests is not known. The rationale for the 3-year interval is that false negatives will be repeated before substantial time elapses, and there is little likelihood that an individual will develop significant complications of diabetes within 3 years of a negative test result.
- Because of the need for follow-up and discussion of abnormal results, testing should be carried out within the health care setting. Community screening outside a health care setting is not recommended because people with positive tests may not seek, or have access to, appropriate follow-up testing and care. Conversely, there may be failure to ensure appropriate repeat testing for individuals who test negative. Community screening may also be poorly targeted, i.e., it may fail to reach the groups most at risk and inappropriately test those at low risk (the worried well) or even those already diagnosed.

Testing for type 2 diabetes in children

- The incidence of type 2 diabetes in adolescents has increased dramatically in the last decade, especially in minority populations, although the disease remains rare in the general pediatric population. Consistent with recommendations for adults, children and youth at increased risk for the presence or the development of type 2 diabetes should be

tested within the health care setting. The recommendations of the ADA consensus statement on type 2 diabetes in children and youth, with some modifications, are summarized here.

Testing for type 2 diabetes in asymptomatic children

Criteria:	Overweight (BMI >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal for height)
Plus any two of the following risk factors:	• Family history of type 2 diabetes in first- or second-degree relative • Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander) • Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small for gestational age birth weight) • Maternal history of diabetes or GDM during the child's gestation
Age of initiation:	Age 10 years or at onset of puberty, if puberty occurs at a younger age
Frequency:	Every 3 years

III. DETECTION AND DIAGNOSIS OF GDM

Recommendations

- Screen for GDM using risk factor analysis and, if appropriate, an OGTT.
- Women with GDM should be screened for diabetes 6–12 weeks postpartum and should be followed up with subsequent screening for the development of diabetes or pre-diabetes.

For many years, GDM has been defined as any degree of glucose intolerance with onset or first recognition during pregnancy.[43] Although most cases resolve with delivery, the definition applied whether the condition persisted after pregnancy and did not exclude the possibility that unrecognized glucose intolerance may have antedated or begun concomitantly with the pregnancy. This definition facilitated a uniform strategy for detection and classification of GDM, but its limitations were recognized for many years. As the ongoing epidemic of obesity and diabetes has led to more type 2 diabetes in women of childbearing age, the number of pregnant women with undiagnosed type 2 diabetes has increased.[44] After deliberations in 2008–2009, the International Association of Diabetes and Pregnancy Study Groups (IADPSG), an international consensus group with representatives from multiple obstetrical and diabetes organizations, including ADA, recommended that high-risk women found to have diabetes at their initial prenatal visit using standard criteria receive a diagnosis of overt, not gestational, diabetes. Approximately 7% of all pregnancies (ranging from 1 to 14% depending on the population studied and the diagnostic tests used) are complicated by GDM, resulting in more than 200,000 cases annually.

Because of the risks of GDM to the mother and neonate, screening and diagnosis are warranted. Current screening and diagnostic strategies, based on the 2004 ADA position statement on GDM[40] are outlined in following table

Screening for and diagnosis of GDM

Women at very high risk should be screened for diabetes as soon as possible after the confirmation of pregnancy. Criteria for very high risk are:

- Severe obesity
- Prior history of GDM or delivery of large-for-gestational-age infant

- Presence of glycosuria
- Diagnosis of PCOS
- Strong family history of type 2 diabetes

Screening/diagnosis at this stage of pregnancy should use standard diagnostic testing.

All women of greater than low risk of GDM, including those above not found to have diabetes early in pregnancy, should undergo GDM testing at 24–28 weeks of gestation. Low-risk status, which does not require GDM screening, is defined as women with ALL of the following characteristics:

- Age <25 years
- Weight normal before pregnancy
- Member of an ethnic group with a low prevalence of diabetes
- No known diabetes in first-degree relatives
- No history of abnormal glucose tolerance
- No history of poor obstetrical outcome

Two approaches may be followed for GDM screening at 24–28 weeks:

1. Two-step approach:
    1. Perform initial screening by measuring plasma or serum glucose 1 h after a 50-g load of ≥140 mg/dl identifies ~80% of women with GDM, while the sensitivity is further increased to ~90% by a threshold of ≥130 mg/dl.
    2. Perform a diagnostic 100-g OGTT on a separate day in women who exceed the chosen threshold on 50-g screening.

2. One-step approach (may be preferred in clinics with high prevalence of GDM): Perform a diagnostic 100-g OGTT in all women to be tested at 24–28 weeks.

The 100-g OGTT should be performed in the morning after an overnight fast of at least 8 h.

To make a diagnosis of GDM, at least two of the following plasma glucose values must be found:

- Fasting ≥95 mg/dl
- 1-h ≥180 mg/dl
- 2-h ≥155 mg/dl

3-h ≥140 mg/dl

Results of the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study, a large-scale (~25,000 pregnant women) multinational epidemiologic study, demonstrated that risk of adverse maternal, fetal, and neonatal outcomes continuously increased as a function of maternal glycemia at 24–28 weeks, even within ranges previously considered normal for pregnancy. For most complications there was no threshold for risk. These results have led to careful reconsideration of the diagnostic criteria for GDM. The IADPSG recommended that all women not known to have prior diabetes undergo a 75-g OGTT at 24–28 weeks of gestation. The group developed diagnostic cut points for the fasting, 1-h, and 2-h PG measurements that conveyed an odds ratio for adverse outcomes of at least 1.75 compared with women with the mean glucose levels in the HAPO study.[43]

Because women with a history of GDM have a greatly increased subsequent risk for diabetes,[45] they should be screened for diabetes 6–12 weeks postpartum, using nonpregnant

OGTT criteria, and should be followed up with subsequent screening for the development of diabetes or pre-diabetes.

PREVENTION/DELAY OF TYPE 2 DIABETES

Recommendations

- Patients with IGT, IFG , or an A1C of 5.7–6.4% should be referred to an effective ongoing support program for weight loss of 5–10% of body weight and an increase in physical activity of at least 150 min/week of moderate activity such as walking.
- Follow-up counseling appears to be important for success.
- Based on potential cost savings of diabetes prevention, such counseling should be covered by third-party payors. In addition to lifestyle counseling, metformin may be considered in those who are at very high risk for developing diabetes (combined IFG and IGT plus other risk factors such as A1C >6%, hypertension, low HDL cholesterol, elevated triglycerides, or family history of diabetes in a first-degree relative) and who are obese and under 60 years of age.
- Monitoring for the development of diabetes in those with pre-diabetes should be performed every year.

Randomized controlled trials have shown that individuals at high risk for developing diabetes (those with IFG, IGT, or both) can be given interventions that significantly decrease the rate of onset of diabetes.[46,47,48]

These interventions include intensive lifestyle modification programs that have been shown to be very effective (58% reduction after 3 years) and use of the pharmacologic agents metformin, α-glucosidase inhibitors, orlistat, and thiazolidinediones, each of which has been shown to decrease incident diabetes to various degrees.

Two studies of lifestyle intervention have shown persistent reduction in the role of conversion to type 2 diabetes with 3 years to 14 years of post intervention follow-up. Based on the results of clinical trials and the known risks of progression of pre-diabetes to diabetes, an ADA Consensus Development Panel 9%[49] concluded that people with IGT and/or IFG should be counseled on lifestyle changes with goals similar to those of the DPP (5–10% weight loss and moderate physical activity of ~30 min/day). Regarding the more difficult issue of drug therapy for diabetes prevention, the consensus panel felt that metformin should be the only drug considered for use in diabetes prevention. For other drugs, the issues of cost, side effects, and lack of persistence of effect in some studies led the panel to not recommend use for diabetes prevention. Metformin use was recommended only for very-high-risk individuals (those with combined IGT and IFG who are obese and have at least one other risk factor for diabetes) who are under 60 years of age. In addition, the panel highlighted the evidence that in the DPP, metformin was most effective compared with lifestyle in individuals with BMI ≥35 kg/m^2 and those under age 60 years.

DIABETES CARE

A. Initial evaluation

A complete medical evaluation should be performed to classify the diabetes, detect the presence of diabetes complications, review previous treatment and glycemic control in patients with established diabetes, assist in formulating a management plan, and provide a basis for continuing care. Laboratory tests appropriate to the evaluation of each patient's medical condition should be performed. A focus on the components of comprehensive care will assist the health care team to ensure optimal management of the patient with diabetes.

Components of the comprehensive diabetes evaluation

Medical history

- Age and characteristics of onset of diabetes (e.g., DKA, asymptomatic laboratory finding)
- Eating patterns, physical activity habits, nutritional status, and weight history; growth and development in children and adolescents
- Diabetes education history
- Review of previous treatment regimens and response to therapy (A1C records)

Current treatment of diabetes, including medications, meal plan, physical activity patterns, and results of glucose monitoring and patient's use of data

- DKA frequency, severity, and cause
- Hypoglycemic episodes

  Hypoglycemia awareness

  Any severe hypoglycemia: frequency and cause
- History of diabetes-related complications

  Microvascular: retinopathy, nephropathy, neuropathy (sensory, including history of foot lesions; autonomic, including sexual dysfunction and gastroparesis)

  Macrovascular: CHD, cerebrovascular disease, PAD

  Other: psychosocial problems, dental disease

Physical examination

- Height, weight, BMI
- Blood pressure determination, including orthostatic measurements when indicated
- Fundoscopic examination

- Thyroid palpation
- Skin examination (for acanthosis nigricans and insulin injection sites)
- Comprehensive foot examination:

  Inspection

  Palpation of dorsalis pedis and posterior tibial pulses

  Presence/absence of patellar and Achilles reflexes

  Determination of proprioception, vibration, and monofilament sensation

Laboratory evaluation

- A1C, if results not available within past 2–3 months
- If not performed/available within past year:

  Fasting lipid profile, including total, LDL- and HDL cholesterol and triglycerides

  Liver function tests

  Test for urine albumin excretion with spot urine albumin/creatinine ratio

  Serum creatinine and calculated GFR

  TSH in type 1 diabetes, dyslipidemia, or women over age 50 years

Referrals

- Annual dilated eye exam
- Family planning for women of reproductive age
- Registered dietitian for MNT
- DSME
- Dental examination
- Mental health professional, if needed

Glycemic control

1. Assessment of glycemic control

Two primary techniques are available for health providers and patients to assess the effectiveness of the management plan on glycemic control: patient self-monitoring of blood glucose (SMBG) or interstitial glucose and A1C.

a. Glucose monitoring

Recommendations

- SMBG should be carried out three or more times daily for patients using multiple insulin injections or insulin pump therapy.
- For patients using less frequent insulin injections, noninsulin therapies, or medical nutrition therapy (MNT) alone, SMBG may be useful as a guide to the success of therapy.
- To achieve postprandial glucose targets, postprandial SMBG may be appropriate.
- When prescribing SMBG, ensure that patients receive initial instruction and routine follow-up evaluation of SMBG technique and using data to adjust therapy.

- Continuous glucose monitoring (CGM) in conjunction with intensive insulin regimens can be a useful tool to lower A1C in selected adults (age ≥25 years) with type 1 diabetes.
- Although the evidence for A1C lowering is less strong in children, teens, and younger adults, CGM may be helpful in these groups. Success correlates with adherence to ongoing use of the device.
- CGM may be a supplemental tool to SMBG in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes.

The ADA consensus and position statements on SMBG provide a comprehensive review of the subject.[50,51] Major clinical trials of insulin-treated patients that demonstrated the benefits of intensive glycemic control on diabetes complications have included SMBG as part of multifactorial interventions, suggesting that SMBG is a component of effective therapy. SMBG allows patients to evaluate their individual response to therapy and assess whether glycemic targets are being achieved. Results of SMBG can be useful in preventing hypoglycemia and adjusting medications (particularly prandial insulin doses), MNT, and physical activity.

The frequency and timing of SMBG should be dictated by the particular needs and goals of the patient. SMBG is especially important for patients treated with insulin in order to monitor for and prevent asymptomatic hypoglycemia and hyperglycemia. For most patients with type 1 diabetes and pregnant women taking insulin, SMBG is recommended three or more times daily. For these populations, significantly more frequent testing may be required to reach A1C targets safely without hypoglycemia. The optimal frequency and timing of SMBG for patients with type 2 diabetes on noninsulin therapy is unclear. A meta-analysis of SMBG in non–insulin-treated patients with type 2 diabetes concluded that some

regimen of SMBG was associated with a reduction in A1C of 0.4%. However, many of the studies in this analysis also included patient education with diet and exercise counseling and, in some cases, pharmacologic intervention, making it difficult to assess the contribution of SMBG alone to improved control.[52] Several recent trials have called into question the clinical utility and cost-effectiveness of routine SMBG in non–insulin-treated patients because the accuracy of SMBG is instrument and user dependent,[53] it is important to evaluate each patient's monitoring technique, both initially and at regular intervals thereafter. In addition, optimal use of SMBG requires proper interpretation of the data. Patients should be taught how to use the data to adjust food intake, exercise, or pharmacological therapy to achieve specific glycemic goals, and these skills should be reevaluated periodically.

CGM through the measurement of interstitial glucose (which correlates well with PG) is available. These sensors require calibration with SMBG, and the latter are still recommended for making acute treatment decisions. CGM devices also have alarms for hypo- and hyperglycemic excursions. Small studies in selected patients with type 1 diabetes have suggested that CGM use reduces the time spent in hypo- and hyperglycemic ranges and may modestly improve glycemic control. A larger 26-week randomized trial of 322 type 1 diabetic patients showed that adults age 25 years and older using intensive insulin therapy and CGM experienced a 0.5% reduction in A1C (from ~7.6 to 7.1%) compared with usual intensive insulin therapy with SMBG. Sensor use in children, teens, and adults to age 24 years did not result in significant A1C lowering, and there was no significant difference in hypoglycemia in any group. Importantly, the greatest predictor of A1C lowering in this study for all age-groups was frequency of sensor use, which was lower in younger age-groups. In a smaller randomized controlled trial of 129 adults and children with baseline

A1C <7.0%, outcomes combining A1C and hypoglycemia favored the group using CGM, suggesting that CGM is also beneficial for individuals with type 1 diabetes who have already achieved excellent control with A1C <7.0%.[54] Although CGM is an evolving technology, emerging data suggest that it may offer benefit in appropriately selected patients who are motivated to wear it most of the time. CGM may be particularly useful in those with hypoglycemia unawareness and/or frequent episodes of hypoglycemia, and studies in this area are ongoing.

b. A1C

Recommendations

- Perform the A1C test at least two times a year in patients who are meeting treatment goals (and who have stable glycemic control).
- Perform the A1C test quarterly in patients whose therapy has changed or who are not meeting glycemic goals.
- Use of point-of-care testing for A1C allows for timely decisions on therapy changes, when needed.

Because A1C is thought to reflect average glycemia over several months and has strong predictive value for diabetes complications[55] A1C testing should be performed routinely in all patients with diabetes, at initial assessment and then as part of continuing care. Measurement approximately every 3 months determines whether a patient's glycemic targets have been reached and maintained. For any individual patient, the frequency of A1C testing should be dependent on the clinical situation, the treatment regimen used, and the judgment of the clinician. Some patients with stable glycemia well within target may do well with testing only twice per year, while unstable or highly intensively managed patients (e.g.,

pregnant type 1 diabetic women) may be tested more frequently than every 3 months. The availability of the A1C result at the time that the patient is seen (point-of-care testing) has been reported to result in increased intensification of therapy and improvement in glycemic control.[56]

The A1C test is subject to certain limitations. Conditions that affect erythrocyte turnover (hemolysis, blood loss) and hemoglobin variants must be considered, particularly when the A1C result does not correlate with the patient's clinical situation.[55] In addition, A1C does not provide a measure of glycemic variability or hypoglycemia. For patients prone to glycemic variability (especially type 1 diabetic patients, or type 2 diabetic patients with severe insulin deficiency), glycemic control is best judged by the combination of results of SMBG testing and the A1C. The A1C may also serve as a check on the accuracy of the patient's meter (or the patient's reported SMBG results) and the adequacy of the SMBG testing schedule.

Following table contains the correlation between A1C levels and mean PG levels based on data from the international A1C-Derived Average Glucose (ADAG) trial using frequent SMBG and CGM in 507 adults (83% Caucasian) with type 1, type 2, and no diabetes.[57] ADA and the American Association of Clinical Chemists have determined that the correlation (r = 0.92) is strong enough to justify reporting both an A1C result and an estimated average glucose (eAG) result when a clinician orders the A1C test. In previous versions of the Standards of Medical Care in Diabetes, the table describing the correlation between A1C and mean glucose was derived from relatively sparse data (one seven-point profile over 1 day per A1C reading) in the primarily Caucasian type 1 participants in the DCCT. [58]

The numbers in the table are now based on ~2,800 readings per A1C in the ADAG trial.

Correlation of A1C with average glucose

A1C (%)	Mean plasma glucose	
	mg/dl	mmol/l
6	126	7.0
7	154	8.6
8	183	10.2
9	212	11.8
10	240	13.4
11	269	14.9
12	298	16.5

- These estimates are based on ADAG data of ~2,700 glucose measurements over 3 months per A1C measurement in 507 adults with type 1, type 2, and no diabetes. The correlation between A1C and average glucose was 0.92 (49). A calculator for converting A1C results into estimated average glucose (eAG), in either mg/dl or mmol/l.

In the ADAG trial, there were no significant differences among racial and ethnic groups in the regression lines between A1C and mean glucose, although there was a trend toward a difference between Africans/African Americans participants and Caucasians that might have been significant had more Africans/African Americans been studied. A recent study comparing A1C to CGM data in 48 type 1 diabetic children found a highly statistically significant correlation between A1C and mean blood glucose, although the correlation (r = 0.7) was significantly lower than in the ADAG trial.[59]

Whether there are significant differences in how A1C relates to average glucose in children or in African American patients is an area for further study. For the time being, the question has not led to different recommendations about testing A1C or different interpretations of the clinical meaning of given levels of A1C in those populations. For patients in whom A1C/eAG and measured blood glucose appear discrepant, clinicians should consider the possibilities of hemoglobinopathy or altered red cell turnover and the options of more frequent and/or different timing of SMBG or use of CGM. Other measures of chronic glycemia such as fructosamine are available, but their linkage to average glucose and their prognostic significance are not as clear as is the case for A1C.

2. Glycemic goals in adults

- Lowering A1C to below or around 7% has been shown to reduce microvascular and neuropathic complications of type 1 and type 2 diabetes. Therefore, for microvascular disease prevention, the A1C goal for nonpregnant adults in general is <7%.
- In type 1 and type 2 diabetes, randomized controlled trials of intensive versus standard glycemic control have not shown a significant reduction in CVD outcomes during the randomized portion of the trials. Long-term follow-up of the DCCT and UK Prospective Diabetes Study (UKPDS) cohorts suggests that treatment to A1C targets below or around 7% in the years soon after the diagnosis of diabetes is associated with long-term reduction in risk of macrovascular disease. Until more evidence becomes available, the general goal of <7% appears reasonable for many adults for macrovascular risk reduction.
- Subgroup analyses of clinical trials such as the DCCT and UKPDS, and evidence for reduced proteinuria in the Action in Diabetes and Vascular Disease: Preterax and

Diamicron Modified Release Controlled Evaluation (ADVANCE) trial suggest a small but incremental benefit in microvascular outcomes with A1C values closer to normal. Therefore, for selected individual patients, providers might reasonably suggest even lower A1C goals than the general goal of <7%, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Such patients might include those with short duration of diabetes, long life expectancy, and no significant CVD.

- Conversely, less-stringent A1C goals than the general goal of <7% may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, and extensive comorbid conditions and those with longstanding diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin.

Glycemic control is fundamental to the management of diabetes. In type 2 diabetes, the Kumamoto study [60,61,62] demonstrated significant reductions in microvascular and neuropathic complications with intensive therapy. Similar to the DCCT-EDIC findings, long-term follow-up of the UKPDS cohort has recently demonstrated a "legacy effect" of early intensive glycemic control on long-term rates of microvascular complications, even with loss of glycemic separation between the intensive and standard cohorts after the end of the randomized controlled trial. The more recent Veterans Affairs Diabetes Trial (VADT) in type 2 diabetes also showed significant reductions in albuminuria with intensive (achieved median A1C 6.9%) compared with standard glycemic control but no difference in retinopathy and neuropathy. In each of these large randomized prospective clinical trials,

treatment regimens that reduced average A1C to 7% (1% above the upper limits of normal) were associated with fewer markers of long-term microvascular complications; however, intensive control was found to increase the risk of severe hypoglycemia and led to weight gain.

Epidemiological analyses of the DCCT and UKPDS demonstrate a curvilinear relationship between A1C and microvascular complications. Such analyses suggest that, on a population level, the greatest number of complications will be averted by taking patients from very poor control to fair or good control. These analyses also suggest that further lowering of A1C from 7 to 6% is associated with further reduction in the risk of microvascular complications, albeit the absolute risk reductions become much smaller. The ADVANCE study of intensive versus standard glycemic control in type 2 diabetes found a statistically significant reduction in albuminuria with an A1C target of <6.5% (achieved median A1C 6.3%) compared with standard therapy achieving a median A1C of 7.0%.[63]

Selected individual patients, especially those with little comorbidity and long life expectancy (who may reap the benefits of further lowering glycemia below 7%) may, adopt glycemic targets as close to normal as possible as long as significant hypoglycemia does not become a barrier.

Whereas many epidemiologic studies and meta-analyses have clearly shown a direct relationship between A1C and CVD, the potential of intensive glycemic control to reduce CVD has been less clearly defined. In the DCCT, there was a trend toward lower risk of CVD events with intensive control (risk reduction 41%, 95% CI 10–68%), but the number of events was small. However, 9-year post-DCCT follow-up of the cohort has shown that participants previously randomized to the intensive arm had a 42% reduction (P = 0.02) in

CVD outcomes and a 57% reduction ($P = 0.02$) in the risk of nonfatal myocardial infarction (MI), stroke, or CVD death compared with participants previously in the standard arm. The benefit of intensive glycemic control in this type 1 diabetic cohort has recently been shown to persist for up to 30 years.

The UKPDS trial of type 2 diabetes observed a 16% reduction in cardiovascular complications (combined fatal or nonfatal MI and sudden death) in the intensive glycemic control arm, although this difference was not statistically significant ($P = 0.052$), and there was no suggestion of benefit on other CVD outcomes such as stroke. In an epidemiologic analysis of the study cohort, a continuous association was observed such that for every percentage point lower median on-study A1C (e.g., 8–7%), there was a statistically significant 18% reduction in CVD events, again with no glycemic threshold. A recent report of 10 years of follow-up of the UKPDS cohort described, for the participants originally randomized to intensive glycemic control compared with those randomized to conventional glycemic control, long-term reductions in MI (15% with sulfonylurea or insulin as initial pharmacotherapy, 33% with metformin as initial pharmacotherapy, both statistically significant) and in all-cause mortality (13 and 27%, respectively, both statistically significant).[64]

Because of ongoing uncertainty regarding whether intensive glycemic control can reduce the increased risk of CVD events in people with type 2 diabetes, several large long-term trials were launched in the past decade to compare the effects of intensive versus standard glycemic control on CVD outcomes in relatively high-risk participants with established type 2 diabetes. In 2008, results of three large trials (ACCORD, ADVANCE, and VADT) suggested no significant reduction in CVD outcomes with intensive glycemic

control in these populations. and their results and implications are reviewed more extensively in a recent ADA position statement.[65]

The ACCORD study randomized 10,251 participants with either history of a CVD event or significant CVD risk to a strategy of intensive glycemic control (target A1C _6.0%) or standard glycemic control (A1C target 7.0 –7.9%) The intensive glycemic control group had more use of insulin in combination with multiple oral agents, significantly more weight gain, and more episodes of severe hypoglycemia than the standard group.

The ADVANCE study randomized participants to a strategy of intensive glycemic control (with primary therapy being the sulfonylurea gliclizide and additional medications as needed to achieve a target A1C of_6.5%) or to standard therapy. ADVANCE participants were slightly older than ACCORD and VADT, had similar high CVD risk. However, they had an average duration of diabetes that was 2 years shorter, lower baseline A1C (median 7.2%), and almost no use of insulin at enrollment. The primary outcome of ADVANCE was a combination of microvascular events (nephropathy and retinopathy)and major adverse cardiovascular events (MI, stroke, and cardiovascular death).Intensive glycemic control significantly reduced the primary end point, although this was due to a significant reduction in the microvascular outcome, primarily development of macroalbuminuria, with no significant reduction in the macrovascular outcome.[63]

VADT randomized participants with type 2 diabetes uncontrolled on insulin or maximal dose oral agents (median entryA1C 9.4%) to a strategy of intensive glycemic control (goal A1C _6.0%) or standard glycemic control, with a planned A1C separation of at least 1.5%.Median A1C levels of 6.9 and 8.4% were achieved in the intensive and standard arms, respectively, within the 1st year of the study. The benefits of intensive glycemic

control on microvascular and neuropathic complications are well established for both type 1 and type 2 diabetes.

Approach to treatment

Therapy for type 2 diabetes

The ADA and the European Association for the Study of Diabetes (EASD) published a consensus statement on the approach to management of hyperglycemia in individuals with type 2 diabetes.[66,67] Highlights of this approach include: intervention at the time of diagnosis with metformin in combination with lifestyle changes (MNT and exercise) and continuing timely augmentation of therapy with additional agents (including early initiation of insulin therapy) as a means of achieving and maintaining recommended levels of glycemic control (i.e., A1C <7% for most patients). The overall objective is to achieve and maintain glycemic control and to change interventions when therapeutic goals are not being met.

The algorithm took into account the evidence for A1C lowering of the individual interventions, their additive effects, and their expense. The precise drugs used and their exact sequence may not be as important as achieving and maintaining glycemic targets safely. Medications not included in the consensus algorithm, owing to less glucose-lowering effectiveness, limited clinical data, and/or relative expense, still may be appropriate choices for individual patients to achieve glycemic goals. Initiation of insulin at the time of diagnosis is recommended for individuals presenting with weight loss or other severe hyperglycemic symptoms or signs.

Medical nutrition therapy (MNT)

General recommendations

- Individuals who have pre-diabetes or diabetes should receive individualized MNT as needed to achieve treatment goals, preferably provided by a registered dietitian familiar with the components of diabetes MNT.
- Because it can result in cost savings and improved outcomes, MNT should be covered by insurance and other payors .

Energy balance, overweight, and obesity

- In overweight and obese insulin-resistant individuals, modest weight loss has been shown to reduce insulin resistance. Thus, weight loss is recommended for all overweight or obese individuals who have or are at risk for diabetes.
- For weight loss, either low-carbohydrate or low-fat calorie-restricted diets may be effective in the short-term (up to 1 year).
- For patients on low-carbohydrate diets, monitor lipid profiles, renal function, and protein intake (in those with nephropathy) and adjust hypoglycemic therapy as needed.
- Physical activity and behavior modification are important components of weight loss programs and are most helpful in maintenance of weight loss.

Primary prevention of diabetes

- Among individuals at high risk for developing type 2 diabetes, structured programs emphasizing lifestyle changes that include moderate weight loss (7% body weight) and regular physical activity (150 min/week) with dietary

strategies including reduced calories and reduced intake of dietary fat can reduce the risk for developing diabetes and are therefore recommended.

- Individuals at high risk for type 2 diabetes should be encouraged to achieve the U.S. Department of Agriculture (USDA) recommendation for dietary fiber (14 g fiber/1,000 kcal) and foods containing whole grains (one-half of grain intake).

Dietary fat intake in diabetes management

- Saturated fat intake should be <7% of total calories.
- Reducing intake of *trans* fat lowers LDL cholesterol and increases HDL cholesterol (A); therefore intake of *trans* fat should be minimized .

Carbohydrate intake in diabetes management

- Monitoring carbohydrate intake, whether by carbohydrate counting, exchanges, or experience-based estimation, remains a key strategy in achieving glycemic control.
- For individuals with diabetes, use of the glycemic index and glycemic load may provide a modest additional benefit for glycemic control over that observed when total carbohydrate is considered alone.

Other nutrition recommendations

- Sugar alcohols and nonnutritive sweeteners are safe when consumed within the acceptable daily intake levels established by the Food and Drug Administration (FDA).
- If adults with diabetes choose to use alcohol, daily intake should be limited to a moderate amount (one drink per day or less for adult women and two drinks per day or less for adult men).

- Routine supplementation with antioxidants, such as vitamins E and C and carotene, is not advised because of lack of evidence of efficacy and concern related to long-term safety.
- Benefit from chromium supplementation in people with diabetes or obesity has not been conclusively demonstrated and therefore cannot be recommended.
- Individualized meal planning should include optimization of food choices to meet recommended dietary allowances (RDAs)/dietary reference intakes (DRIs) for all micronutrients.

MNT is an integral component of diabetes prevention, management, and self-management education. In addition to its role in preventing and controlling diabetes, ADA recognizes the importance of nutrition as an essential component of an overall healthy lifestyle. A full review of the evidence regarding nutrition in preventing and controlling diabetes and its complications and additional nutrition-related recommendations can be found in the ADA position statement, Nutrition Recommendations and Interventions for Diabetes, published in 2006 and updated for 2008.[68] Achieving nutrition-related goals requires a coordinated team effort that includes the active involvement of the person with pre-diabetes or diabetes. Because of the complexity of nutrition issues, it is recommended that a registered dietitian who is knowledgeable and skilled in implementing nutrition therapy into diabetes management and education be the team member who provides MNT.

Clinical trials/outcome studies of MNT have reported decreases in A1C at 3–6 months ranging from 0.25 to 2.9% with higher reductions seen in type 2 diabetes of shorter duration. Multiple studies have demonstrated sustained improvements in A1C at 12 months

and longer when a registered dietitian provided follow-up visits ranging from monthly to three sessions per year.[69,70] Meta-analyses of studies in nondiabetic, free-living subjects report that MNT reduces LDL cholesterol by 15–25 mg/dl or by up to 16%, while clinical trials support a role for lifestyle modification in treating hypertension. Because of the effects of obesity on insulin resistance, weight loss is an important therapeutic objective for overweight or obese individuals with pre-diabetes or diabetes.[71] Short-term studies have demonstrated that moderate weight loss (5% of body weight) in subjects with type 2 diabetes is associated with decreased insulin resistance, improved measures of glycemia and lipemia, and reduced blood pressure.[72] longer-term studies (≥52 weeks) showed mixed effects on A1C in adults with type 2 diabetes[73] and results were confounded by pharmacologic weight loss therapy. A systematic review of 80 weight loss studies of ≥1 year duration demonstrated that moderate weight loss achieved through diet alone, diet and exercise, and meal replacements can be achieved and maintained over the long term (4.8–8% weight loss at 12 months)[74] The multifactorial intensive lifestyle intervention used in the DPP, which included reduced intake of fat and calories, led to weight loss averaging 7% at 6 months and maintenance of 5% weight loss at 3 years, associated with a 58% reduction in incidence of type 2 diabetes.[75] Look AHEAD (Action for Health in Diabetes) is a large clinical trial designed to determine whether long-term weight loss will improve glycemia and prevent cardiovascular events in subjects with type 2 diabetes. One-year results of the intensive lifestyle intervention in this trial show an average of 8.6% weight loss, significant reduction of A1C, and reduction in several CVD risk factors.[76]

The optimal macronutrient distribution of weight loss diets has not been established. Although low-fat diets have traditionally been promoted for weight loss, several randomized

controlled trials found that subjects on low-carbohydrate diets (<130 g/day of carbohydrate) lost more weight at 6 months than subjects on low-fat diets[77] however, at 1 year, the difference in weight loss between the low-carbohydrate and low-fat diets was not significant and weight loss was modest with both diets. Another study of overweight women randomized to one of four diets showed significantly more weight loss at 12 months with the Atkins low-carbohydrate diet than with higher-carbohydrate diets.[78]

Changes in serum triglyceride and HDL cholesterol were more favorable with the low-carbohydrate diets. In one study, those subjects with type 2 diabetes demonstrated a greater decrease in A1C with a low-carbohydrate diet than with a low-fat diet.[79] A recent meta-analysis showed that at 6 months, low-carbohydrate diets were associated with greater improvements in triglyceride and HDL cholesterol concentrations than low-fat diets; however, LDL cholesterol was significantly higher with the low-carbohydrate diets.[80]

The RDA for digestible carbohydrate is 130 g/day and is based on providing adequate glucose as the required fuel for the central nervous system without reliance on glucose production from ingested protein or fat. Although brain fuel needs can be met on lower-carbohydrate diets, long-term metabolic effects of very-low-carbohydrate diets are unclear, and such diets eliminate many foods that are important sources of energy, fiber, vitamins, and minerals that are important in dietary palatability. Although numerous studies have attempted to identify the optimal mix of macronutrients for meal plans of people with diabetes, it is unlikely that one such combination of macronutrients exists. The best mix of carbohydrate, protein, and fat appears to vary depending on individual circumstances. For those individuals seeking guidance as to macronutrient distribution in healthy adults, DRIs may be helpful.[43] Regardless of the macronutrient mix, the total caloric intake must be

appropriate to the weight management goal. Further, individualization of the macronutrient composition will depend on the metabolic status of the patient (e.g., lipid profile and renal function) and/or food preferences. Plant-based diets (vegan or vegetarian) that are well planned and nutritionally adequate have also been shown to improve metabolic control.[43]

The primary goal with respect to dietary fat in individuals with diabetes is to limit saturated fatty acids, *trans* fatty acids, and cholesterol intake so as to reduce risk for CVD. Saturated and *trans* fatty acids are the principal dietary determinants of plasma LDL cholesterol. There is a lack of evidence on the effects of specific fatty acids on people with diabetes; therefore, the recommended goals are consistent with those for individuals with CVD.[43]

Reduced calorie sweeteners approved by the FDA include sugar alcohols (polyols) such as erythritol, isomalt, lactitol, maltitol, mannitol, sorbitol, xylitol, tagatose, and hydrogenated starch hydrolysates. The use of sugar alcohols appears to be safe; however, they may cause diarrhea, especially in children. Stevia (Rebaudioside A) has been designated by the FDA as being generally recognized as safe (GRAS).

Bariatric surgery

Recommendations

- Bariatric surgery should be considered for adults with BMI >35 kg/m^2 and type 2 diabetes, especially if the diabetes or associated comorbidities are difficult to control with lifestyle and pharmacologic therapy. Patients with type 2 diabetes who have undergone bariatric surgery need life-long lifestyle support and medical monitoring.
- Although small trials have shown glycemic benefit of bariatric surgery in patients with type 2 diabetes and BMI of 30–35 kg/m^2, there is currently insufficient evidence to

generally recommend surgery in patients with BMI <35 kg/m^2 outside of a research protocol.

- The long-term benefits, cost-effectiveness, and risks of bariatric surgery in individuals with type 2 diabetes should be studied in well-designed, randomized controlled trials with optimal medical and lifestyle therapy as the comparator.

Gastric reduction surgery, either gastric banding or procedures that involve bypassing or transposing sections of the small intestine, when part of a comprehensive team approach, can be an effective weight loss treatment for severe obesity, and national guidelines support its consideration for people with type 2 diabetes who have BMI >35 kg/m^2. Bariatric surgery has been shown to lead to near or complete normalization of glycemia in ~55–95% of patients with type 2 diabetes, depending on the surgical procedure. A meta-analysis of studies of bariatric surgery reported that 78% of individuals with type 2 diabetes had complete "resolution" of diabetes (normalization of blood glucose levels in the absence of medications) and that the resolution rates were sustained in studies that had follow-up exceeding 2 years.[81]

Resolution rates are lower with procedures that only constrict the stomach and higher with those that bypass portions of the small intestine. Additionally, there is a suggestion that intestinal bypass procedures may have glycemic effects that are independent of their effects on weight.

A recent randomized controlled trial compared adjustable gastric banding to the "best available" medical and lifestyle therapy in subjects with type 2 diabetes diagnosed <2 years before randomization and with BMI 30–40 kg/m^2. [82]

In this trial, 73% of surgically treated patients achieved "remission" of their diabetes, compared with 13% of those treated medically. The latter group lost only 1.7% of body weight, suggesting that their therapy was not optimal. Overall the trial had 60 subjects, and only 13 had a BMI <35 kg/m^2, making it difficult to generalize these results to diabetic patients who are less severely obese or with longer duration of diabetes.

Bariatric surgery is costly in the short term and has some risks. Rates of morbidity and mortality directly related to the surgery have been reduced considerably in recent years, with 30-day mortality rates now 0.28%, similar to those of laparoscopic cholecystectomy . Longer-term concerns include vitamin and mineral deficiencies, osteoporosis, and rare but often severe hypoglycemia from insulin hypersecretion. Cohort studies attempting to match subjects suggest that the procedure may reduce longer-term mortality rates, and it is reasonable to postulate that there may be recouping of costs over the long term. However, studies of the mechanisms of glycemic improvement, long-term benefits and risks, and cost-effectiveness of bariatric surgery in individuals with type 2 diabetes will require well-designed, randomized clinical trials with optimal medical and lifestyle therapy of diabetes and cardiovascular risk factors as the comparators.[43]

Diabetes self-management education

Recommendations

- People with diabetes should receive DSME according to national standards when their diabetes is diagnosed and as needed thereafter.
- Effective self-management and quality of life are the key outcomes of DSME and should be measured and monitored as part of care.
- DSME should address psychosocial issues, since emotional well-being is associated with positive diabetes outcomes.

- Because DSME can result in cost-savings and improved outcomes, DSME should be reimbursed by third-party payors.

DSME is an essential element of diabetes care, and national standards for DSME are based on evidence for its benefits.[83] Education helps people with diabetes initiate effective self-management and cope with diabetes when they are first diagnosed. Ongoing DSME and support also help people with diabetes maintain effective self-management throughout a lifetime of diabetes as they face new challenges and as treatment advances become available. DSME helps patients optimize metabolic control, prevent and manage complications, and maximize quality of life in a cost-effective manner.[84]

DSME is the on-going process of facilitating the knowledge, skill, and ability necessary for diabetes self-care. This process incorporates the needs, goals, and life experiences of the person with diabetes. The overall objectives of DSME are to support informed decision-making, self-care behaviors, problem-solving, and active collaboration with the health care team and to improve clinical outcomes, health status, and quality of life in a cost-effective manner. Current best practice of DSME is a skills-based approach that focuses on helping those with diabetes make informed self-management choices. DSME has changed from a didactic approach focusing on providing information, to a more theoretically based empowerment model that focuses on helping those with diabetes make informed self-management decisions. Care of diabetes has shifted to an approach that is more patient centered and places the person with diabetes at the center of the care model working in collaboration with health care professionals. Patient-centered care is respectful of and responsive to individual.

Multiple studies have found that DSME is associated with improved diabetes knowledge and self-care behavior.[85]

Both individual and group approaches have been found effective.

Diabetes education is associated with increased use of primary and preventive services and lower use of acute, inpatient hospital services.[86] Patients who participate in diabetes education are more likely to follow best practice treatment recommendations, particularly among the medicare population, and to have lower Medicare and commercial claim costs.[87]

National Standards for DSME

The National Standards for DSME are designed to define quality diabetes self-management education and to assist diabetes educators in a variety of settings to provide evidence-based education. The standards, most recently revised in 2007, are reviewed and updated every 5 years by a task force representing key organizations involved in the field of diabetes education and care.

Physical activity

Recommendations

- People with diabetes should be advised to perform at least 150 min/week of moderate-intensity aerobic physical activity (50–70% of maximum heart rate).
- In the absence of contraindications, people with type 2 diabetes should be encouraged to perform resistance training three times per week.

ADA technical reviews on exercise in patients with diabetes, currently being updated, have summarized the value of exercise in the diabetes management plan.[88] Regular exercise has been shown to improve blood glucose control, reduce cardiovascular risk factors, contribute to weight loss, and improve well being. Furthermore, regular exercise may prevent type 2 diabetes in high-risk individuals.

Frequency and type of exercise

The U.S. Department of Health and Human Services' Physical Activity Guidelines for Americans suggest that adults over age 18 years perform 150 min/week of moderate-intensity or 75 min/week of vigorous aerobic physical activity or an equivalent combination of the two. In addition, the guidelines suggest that adults also do muscle-strengthening activities that involve all major muscle groups two or more days per week. The guidelines suggest that adults over age 65 years, or those with disabilities, follow the adult guidelines if possible or (if this is not possible) be as physically active as they are able.[89] Based on the studies it seems reasonable to recommend that people with diabetes try to follow the physical activity guidelines for the general population.

Progressive resistance exercise improves insulin sensitivity in older men with type 2 diabetesased on the studies to the same or even to a greater extent as aerobic exercise. Clinical trials have provided strong evidence for the A1C-lowering value of resistance training in older adults with type 2 diabetes and for an additive benefit of combined aerobic and resistance exercise in adults with type 2 diabetes.[43]

Evaluation of the diabetic patient before recommending an exercise program

Prior guidelines have suggested that before recommending a program of physical activity, the provider should assess patients with multiple cardiovascular risk factors for coronary artery disease (CAD). Recent ADA consensus statement on this issue concluded that routine screening is not recommended. Providers should use clinical judgment in this area. Certainly, high-risk patients should be encouraged to start with short periods of low-intensity exercise and to increase the intensity and duration slowly.[90] Providers should assess patients for conditions that might contraindicate certain types of exercise or

predispose to injury, such as uncontrolled hypertension, severe autonomic neuropathy, severe peripheral neuropathy or history of foot lesions, and unstable proliferative retinopathy. The patient's age and previous physical activity level should be considered.[43]

Exercise in the presence of non optimal glycemic control

a. Hyperglycemia.

When people with type 1 diabetes are deprived of insulin for 12–48 h and are ketotic, exercise can worsen hyperglycemia and ketosis ; therefore, vigorous activity should be avoided in the presence of ketosis. However, it is not necessary to postpone exercise simply based on hyperglycemia, provided the patient feels well and urine and/or blood ketones are negative.[91]

b. Hypoglycemia.

In individuals taking insulin and/or insulin secretagogues, physical activity can cause hypoglycemia if medication dose or carbohydrate consumption is not altered. For individuals on these therapies, added carbohydrate should be ingested if pre-exercise glucose levels are <100 mg/dl (5.6 mmol/l). Hypoglycemia is rare in diabetic individuals who are not treated with insulin or insulin secretagogues, and no preventive measures for hypoglycemia are usually advised in these cases.[40]

Exercise in the presence of specific long-term complications of diabetes

a. Retinopathy.

In the presence of proliferative diabetic retinopathy (PDR) or severe non-proliferative diabetic retinopathy (NPDR), vigorous aerobic or resistance exercise may be contraindicated because of the risk of triggering vitreous hemorrhage or retinal detachment.[43]

b. Peripheral neuropathy.

Decreased pain sensation in the extremities results in increased risk of skin breakdown and infection and of Charcot joint destruction. Prior recommendations have advised non–weight-bearing exercise for patients with severe peripheral neuropathy. Studies have shown that moderate-intensity walking may not lead to increased risk of foot ulcers or reulceration in those with peripheral neuropathy. All individuals with peripheral neuropathy should wear proper footwear and examine their feet daily for early detection of lesions. Anyone with a foot injury or open sore should be restricted to non–weight-bearing activities.[43]

c. Autonomic neuropathy.

Autonomic neuropathy can increase the risk of exercise-induced injury or adverse events through decreased cardiac responsiveness to exercise, postural hypotension, impaired thermoregulation, impaired night vision due to impaired papillary reaction, and unpredictable carbohydrate delivery from gastroparesis predisposing to hypoglycemia. Autonomic neuropathy is also strongly associated with CVD in people with diabetes. People with diabetic autonomic neuropathy should undergo cardiac investigation before beginning physical activity more intense than that to which they are accustomed.[43]

d. Albuminuria and nephropathy.

Physical activity can acutely increase urinary protein excretion. However, there is no evidence that vigorous exercise increases the rate of progression of diabetic kidney disease and likely no need for any specific exercise restrictions for people with diabetic kidney disease.[43]

Psychosocial assessment and care

Recommendations

- Assessment of psychological and social situation should be included as an ongoing part of the medical management of diabetes.
- Psychosocial screening and follow-up should include, but is not limited to, attitudes about the illness, expectations for medical management and outcomes, affect/mood, general and diabetes-related quality of life, resources (financial, social, and emotional), and psychiatric history.
- Screen for psychosocial problems such as depression and diabetes-related distress, anxiety, eating disorders, and cognitive impairment when self-management is poor.

Psychological and social problems can impair the ability of the individual or the family to carry out diabetes care tasks and therefore compromise health status. There are opportunities for the clinician to assess psychosocial status in a timely and efficient manner so that referral for appropriate services can be accomplished.

Key opportunities for screening of psychosocial status occur at diagnosis, during regularly scheduled management visits, during hospitalizations, at discovery of complications, or when problems with glucose control, quality of life, or adherence are identified. Patients are likely to exhibit psychological vulnerability at diagnosis and when their medical status changes, i.e., the end of the honeymoon period, when the need for intensified treatment is evident, and when complications are discovered.[43]

Issues known to impact self-management and health outcomes include but are not limited to: attitudes about the illness, expectations for medical management and outcomes, affect/mood, general and diabetes-related quality of life, diabetes-related distress,[92]

resources (financial, social, and emotional), and psychiatric history. Screening tools are available for a number of these areas. Indications for referral to a mental health specialist familiar with diabetes management may include gross noncompliance with medical regimen (by self or others) depression with the possibility of self-harm, debilitating anxiety (alone or with depression), indications of an eating disorder, or cognitive functioning that significantly impairs judgment. It is preferable to incorporate psychological assessment and treatment into routine care rather than waiting for identification of a specific problem or deterioration in psychological status. Although the clinician may not feel qualified to treat psychological problems, using the patient-provider relationship as a foundation for further treatment can increase the likelihood that the patient will accept referral for other services. It is important to establish that emotional well-being is part of diabetes management.

When treatment goals are not met

For a variety of reasons, some people with diabetes and their health care providers do not achieve the desired goals of treatment. Rethinking the treatment regimen may require assessment of barriers including income, health literacy, diabetes distress, depression, and competing demands, including those related to family responsibilities and dynamics. Other strategies may include culturally appropriate and enhanced DSME, co-management with a diabetes team, referral to a medical social worker for assistance with insurance coverage, or change in pharmacological therapy. Initiation of or increase in SMBG, utilization of CGM, frequent contact with the patient, or referral to a mental health professional or physician with special expertise in diabetes may be useful. Providing patients with an algorithm for self-titration of insulin doses based on SMBG results may be helpful for type 2 patients who take insulin.[43]

Intercurrent illness

The stress of illness, trauma, and/or surgery frequently aggravates glycemic control and may precipitate diabetic ketoacidosis (DKA) or nonketotic hyperosmolar state, life-threatening conditions that require immediate medical care to prevent complications and death. Any condition leading to deterioration in glycemic control necessitates more frequent monitoring of blood glucose and (in ketosis-prone patients) urine or blood ketones. Marked hyperglycemia requires temporary adjustment of the treatment program and, if accompanied by ketosis, vomiting, or alteration in level of consciousness, immediate interaction with the diabetes care team. The patient treated with noninsulin therapies or MNT alone may temporarily require insulin. Adequate fluid and caloric intake must be assured. Infection or dehydration are more likely to necessitate hospitalization of the person with diabetes than the person without diabetes.

The hospitalized patient should be treated by a physician with expertise in the management of diabetes.[43]

Hypoglycemia

Recommendations

- Glucose (15–20 g) is the preferred treatment for the conscious individual with hypoglycemia, although any form of carbohydrate that contains glucose may be used. If SMBG 15 min after treatment shows continued hypoglycemia, the treatment should be repeated. Once SMBG glucose returns to normal, the individual should consume a meal or snack to prevent recurrence of hypoglycemia.
- Glucagon should be prescribed for all individuals at significant risk of severe hypoglycemia, and caregivers or family members of these individuals should be

instructed in its administration. Glucagon administration is not limited to health care professionals.

- Individuals with hypoglycemia unawareness or one or more episodes of severe hypoglycemia should be advised to raise their glycemic targets to strictly avoid further hypoglycemia for at least several weeks to partially reverse hypoglycemia unawareness and reduce risk of future episodes.

Hypoglycemia is the leading limiting factor in the glycemic management of type 1 and insulin-treated type 2 diabetes.[93] Treatment of hypoglycemia (PG <70 mg/dl) requires ingestion of glucose- or carbohydrate-containing foods. The acute glycemic response correlates better with the glucose content than with the carbohydrate content of the food. Although pure glucose is the preferred treatment, any form of carbohydrate that contains glucose will raise blood glucose. Added fat may retard and then prolong the acute glycemic response. Ongoing activity of insulin or insulin secretagogues may lead to recurrence of hypoglycemia unless further food is ingested after recovery.

Severe hypoglycemia (where the individual requires the assistance of another person and cannot be treated with oral carbohydrate due to confusion or unconsciousness) should be treated using emergency glucagon kits, which require a prescription. Those in close contact with or who have custodial care of people with hypoglycemia-prone diabetes (family members, roommates, school personnel, child care providers, correctional institution staff, or coworkers) should be instructed in use of such kits. An individual does not need to be a health care professional to safely administer glucagon. Care should be taken to ensure that unexpired glucagon kits are available.

Prevention of hypoglycemia is a critical component of diabetes management. Teaching people with diabetes to balance insulin use, carbohydrate intake, and exercise is a

necessary but not always sufficient strategy. In type 1 diabetes and severely insulin-deficient type 2 diabetes, the syndrome of hypoglycemia unawareness, or hypoglycemia-associated autonomic failure, can severely compromise stringent diabetes control and quality of life. The deficient counter-regulatory hormone release and autonomic responses in this syndrome are both risk factors for and are caused by hypoglycemia. A corollary to this "vicious cycle" is that several weeks of avoidance of hypoglycemia has been demonstrated to improve counter-regulation and awareness to some extent in many patients.[43] Hence, patients with one or more episodes of severe hypoglycemia may benefit from at least short-term relaxation of glycemic targets.

Immunization

Recommendations

- Annually provide an influenza vaccine to all diabetic patients ≥6 months of age.
- Administer pneumococcal polysaccharide vaccine to all diabetic patients ≥2 years of age. A one-time revaccination is recommended for individuals >64 years of age previously immunized when they were <65 years of age if the vaccine was administered >5 years ago. Other indications for repeat vaccination include nephrotic syndrome, chronic renal disease, and other immunocompromised states, such as after transplantation.

Influenza and pneumonia are common, preventable infectious diseases associated with high mortality and morbidity in the elderly and in people with chronic diseases. Though there are limited studies reporting the morbidity and mortality of influenza and pneumococcal pneumonia specifically in people with diabetes, observational studies of patients with a variety of chronic illnesses, including diabetes, show that these conditions are

associated with an increase in hospitalizations for influenza and its complications. People with diabetes may be at increased risk of the bacteremic form of pneumococcal infection and have been reported to have a high risk of nosocomial bacteremia, which has a mortality rate as high as 50%.[94]

Safe and effective vaccines are available that can greatly reduce the risk of serious complications from these diseases. In a case-control series, influenza vaccine was shown to reduce diabetes-related hospital admission by as much as 79% during flu epidemics. There is sufficient evidence to support that people with diabetes have appropriate serologic and clinical responses to these vaccinations. The Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices recommends influenza and pneumococcal vaccines for all individuals with diabetes.[95]

PREVENTION AND MANAGEMENT OF DIABETES COMPLICATIONS

A. Cardiovascular disease

CVD is the major cause of morbidity and mortality for individuals with diabetes and the largest contributor to the direct and indirect costs of diabetes. The common conditions coexisting with type 2 diabetes (e.g., hypertension and dyslipidemia) are clear risk factors for CVD, and diabetes itself confers independent risk. Numerous studies have shown the efficacy of controlling individual cardiovascular risk factors in preventing or slowing CVD in people with diabetes. Large benefits are seen when multiple risk factors are addressed globally Risk for coronary heart disease and CVD in general can be estimated using multivariable risk factor approaches, and such a strategy may be desirable to undertake in adult patients prior to instituting preventive therapy.[96]

1 Hypertension/blood pressure control

Hypertension is a common comorbidity of diabetes that affects the majority of patients, with prevalence depending on type of diabetes, age, obesity, and ethnicity. Hypertension is a major risk factor for both CVD and microvascular complications. In type 1 diabetes, hypertension is often the result of underlying nephropathy, while in type 2 diabetes it usually coexists with other cardiometabolic risk factors.

Recommendations

Screening and diagnosis

- Blood pressure should be measured at every routine diabetes visit. Patients found to have systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥80 mmHg should have blood pressure confirmed on a separate day. Repeat systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥80 mmHg confirms a diagnosis of hypertension.

Goals

- Patients with diabetes should be treated to a systolic blood pressure <130 mmHg.
- Patients with diabetes should be treated to a diastolic blood pressure <80 mmHg.

Treatment

- Patients with a systolic blood pressure 130–139 mmHg or a diastolic blood pressure 80–89 mmHg may be given lifestyle therapy alone for a maximum of 3 months, and then if targets are not achieved, patients should be treated with the addition of pharmacological agents.
- Patients with more severe hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg) at diagnosis or follow-up should receive pharmacologic therapy in addition to lifestyle therapy.

- Lifestyle therapy for hypertension consists of weight loss if overweight, DASH-style dietary pattern including reducing sodium and increasing potassium intake, moderation of alcohol intake, and increased physical activity.
- Pharmacologic therapy for patients with diabetes and hypertension should be paired with a regimen that includes either an ACE inhibitor or an angiotensin II receptor blocker (ARB). If one class is not tolerated, the other should be substituted. If needed to achieve blood pressure targets, a thiazide diuretic should be added to those with an estimated glomerular filtration rate (GFR) (see below) ≥30 ml · min/1.73 m^2 and a loop diuretic for those with an estimated GFR <30 ml · min/1.73 m^2.
- Multiple drug therapy (two or more agents at maximal doses) is generally required to achieve blood pressure targets.
- If ACE inhibitors, ARBs, or diuretics are used, kidney function and serum potassium levels should be closely monitored.
- In pregnant patients with diabetes and chronic hypertension, blood pressure target goals of 110–129/65–79 mmHg are suggested in the interest of long-term maternal health and minimizing impaired fetal growth. ACE inhibitors and ARBs are contraindicated during pregnancy.

Because of the clear synergistic risks of hypertension and diabetes, the diagnostic cutoff for a diagnosis of hypertension is lower in people with diabetes (blood pressure ≥130/80 mmHg) than in those without diabetes (blood pressure ≥140/90 mmHg) in type 2 patients with significant nephropathy, ARBs were superior to calcium channel blockers for reducing heart failure. During pregnancy in diabetic women with chronic hypertension, target blood pressure goals of 110–129 mmHg systolic and 65–79 mmHg diastolic are

reasonable, as they contribute to long-term maternal health. Lower blood pressure levels may be associated with impaired fetal growth. During pregnancy, treatment with ACE inhibitors and ARBs is contraindicated, since they can cause fetal damage.[97]

2. Dyslipidemia/lipid management

Recommendations

Screening

- In most adult patients, measure fasting lipid profile at least annually. In adults with low-risk lipid values (LDL cholesterol <100 mg/dl, HDL cholesterol >50 mg/dl, and triglycerides <150 mg/dl), lipid assessments may be repeated every 2 years.

Treatment recommendations and goals

- Lifestyle modification focusing on the reduction of saturated fat, *trans* fat, and cholesterol intake; increase of n-3 fatty acids, viscous fiber, and plant stanols/sterols; weight loss (if indicated); and increased physical activity should be recommended to improve the lipid profile in patients with diabetes.
- Statin therapy should be added to lifestyle therapy, regardless of baseline lipid levels, for diabetic patients: with overt CVD and without CVD who are over the age of 40 years and have one or more other CVD risk factors.
- For patients at lower risk than described above (e.g., without overt CVD and under the age of 40 years), statin therapy should be considered in addition to lifestyle therapy if LDL cholesterol remains >100 mg/dl or in those with multiple CVD risk factors.
- In individuals without overt CVD, the primary goal is an LDL cholesterol <100 mg/dl (2.6 mmol/l).

- In individuals with overt CVD, a lower LDL cholesterol goal of <70 mg/dl (1.8 mmol/l), using a high dose of a statin, is an option.
- If drug-treated patients do not reach the above targets on maximal tolerated statin therapy, a reduction in LDL cholesterol of ~30–40% from baseline is an alternative therapeutic goal.
- Triglycerides levels <150 mg/dl (1.7 mmol/l) and HDL cholesterol >40 mg/dl (1.0 mmol/l) in men and >50 mg/dl (1.3 mmol/l) in women, are desirable. However, LDL cholesterol–targeted statin therapy remains the preferred strategy.
- If targets are not reached on maximally tolerated doses of statins, combination therapy using statins and other lipid-lowering agents may be considered to achieve lipid targets but has not been evaluated in outcome studies for either CVD outcomes or safety.
- Statin therapy is contraindicated in pregnancy.

a. Evidence for benefits of lipid-lowering therapy.

Patients with type 2 diabetes have an increased prevalence of lipid abnormalities, contributing to their high risk of CVD. Over the past decade or more, multiple clinical trials have demonstrated significant effects of pharmacologic (primarily statin) therapy on CVD outcomes in subjects with CHD and for primary CVD prevention.[98] Analyses of diabetic subgroups of larger trials and trials specifically in subjects with diabetes.[99] showed significant primary and secondary prevention of CVD events with and without CHD deaths in diabetic populations. Low levels of HDL cholesterol, often associated with elevated triglyceride levels, are the most prevalent pattern of dyslipidemia in people with type 2 diabetes.

b. Dyslipidemia treatment and target lipid levels.

For most patients with diabetes, the first priority of dyslipidemia therapy (unless severe hypertriglyceridemia is the immediate issue) is to lower LDL cholesterol to a target goal of <100 mg/dl (2.60 mmol/l). Lifestyle intervention, including MNT, increased physical activity, weight loss, and smoking cessation, may allow some patients to reach lipid goals. Nutrition intervention should be tailored according to each patient's age, type of diabetes, pharmacological treatment, lipid levels, and other medical conditions and should focus on the reduction of saturated fat, cholesterol, and *trans* unsaturated fat intake and increases in n-3 fatty acids, viscous fiber (such as in oats, legumes, citrus), and plant stanols/sterols. Glycemic control can also beneficially modify plasma lipid levels, particularly in patients with very high triglycerides and poor glycemic control.

In those with clinical CVD or who are over age 40 years and have CVD risk factors, pharmacological treatment should be added to lifestyle therapy regardless of baseline lipid levels. Statins are the drugs of choice for lowering LDL cholesterol.

In patients other than those described above, statin treatment should be considered if there is an inadequate LDL cholesterol response to lifestyle modifications and improved glucose control or if the patient has increased cardiovascular risk (e.g., multiple cardiovascular risk factors or long duration of diabetes). Very little clinical trial evidence exists for type 2 diabetic patients under the age of 40 years and for type 1 diabetic patients of any age. In the Heart Protection Study (lower age limit 40 years), the subgroup of 600 patients with type 1 diabetes had a proportionately similar reduction in risk as patients with type 2 diabetes although not statistically significant. Although the data are not definitive, consideration should be given to lipid-lowering goals for type 1 diabetic patients similar to those for type 2 diabetic patients, particularly if other cardiovascular risk factors are present.[100]

Following are the summary of recommendations for glycemic, blood pressure, and lipid control for adults with diabetes,

A1C <7.0%*

Blood pressure <130/80 mmHg

Lipids

LDL cholesterol <100 mg/dl (<2.6 mmol/l)†

Antiplatelet agents

Recommendations

- Consider aspirin therapy (75–162 mg/day) as a primary prevention strategy in those with type 1 or type 2 diabetes at increased cardiovascular risk (10-year risk >10%). This includes most men >50 years of age or women >60 years of age who have at least one additional major risk factor (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria).
- There is not sufficient evidence to recommend aspirin for primary prevention in lower risk individuals, such as men <50 years of age or women <60 years of age without other major risk factors. For patients in these age-groups with multiple other risk factors, clinical judgment is required.
- Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in those with diabetes with a history of CVD.
- For patients with CVD and documented aspirin allergy, clopidogrel (75 mg/day) should be used.
- Combination therapy with ASA (75–162 mg/day) and clopidogrel (75 mg/day) is reasonable for up to a year after an acute coronary syndrome.

ADA and the American Heart Association (AHA) have, in the past, jointly recommended that low-dose aspirin therapy be used as a primary prevention strategy in those with diabetes at increased cardiovascular risk, including those who are over 40 years of age or those with additional risk factors (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria).These recommendations were derived from several older trials that included small numbers of patients with diabetes.[96] Aspirin has been shown to be effective in reducing cardiovascular morbidity and mortality in high-risk patients with previous MI or stroke (secondary prevention). Its net benefit in primary prevention among patients with no previous cardiovascular events is more controversial, both for patients with and without a history of diabetes. The U.S. Preventive Services Task Force recently updated its evidence base and recommendations about aspirin use for primary prevention. The Task Force recommended encouraging aspirin use in men 45–79 and women 55–79 years of age and not encouraging aspirin use in younger adults and did not differentiate based on the presence or absence of diabetes.

Average daily dosages used in most clinical trials involving patients with diabetes ranged from 50–650 mg but were mostly in the range of 100–325 mg/day. There is little evidence to support any specific dose, but using the lowest possible dosage may help reduce side effects.[101] Although platelets from patients with diabetes have altered function, it is unclear what, if any, impact that finding has on the required dose of aspirin for cardioprotective effects in the patient with diabetes. Many alternate pathways for platelet activation exist that are independent of thromboxane A_2 and thus not sensitive to the effects of aspirin. Therefore, while "aspirin resistance" appears higher in diabetic patients when measured by a variety of ex vivo and in vitro methods (platelet aggrenometry, measurement

of thromboxane B_2), these observations alone are insufficient to empirically recommend that higher doses of aspirin be used in the diabetic patient.[43]

Aspirin use for secondary prevention continues to have a strong evidence base and is recommended. Until further evidence is available, low-dose (75–162 mg/day) aspirin use for primary prevention is reasonable for adults with diabetes and no previous history of vascular disease who are at increased CVD risk (10-year risk of CVD events >10%) and who are not at increased risk for bleeding. This generally includes most men over age 50 years and women over age 60 years who also have one or more of the following major risk factors: smoking, hypertension, dyslipidemia, family history of premature CVD, and albuminuria.

4. Smoking cessation

Recommendations

- Advise all patients not to smoke.
- Include smoking cessation counseling and other forms of treatment as a routine component of diabetes care.

Issues of smoking and diabetes are reviewed in detail in the ADA technical review.[102] and position statement on this topic. A large body of evidence from epidemiological, case-control, and cohort studies provides convincing documentation of the causal link between cigarette smoking and health risks. Cigarette smoking contributes to one of every five deaths in the U.S. and is the most important modifiable cause of premature death. Much of the prior work documenting the impact of smoking on health did not separately discuss results on subsets of individuals with diabetes, suggesting that the identified risks are at least equivalent to those found in the general population. Other studies of individuals with diabetes consistently found a heightened risk of CVD and premature

death among smokers. Smoking is also related to the premature development of microvascular complications of diabetes and may have a role in the development of type 2 diabetes.

A number of large randomized clinical trials have demonstrated the efficacy and cost-effectiveness of smoking cessation counseling in changing smoking behavior and reducing tobacco use. The routine and thorough assessment of tobacco use is important as a means of preventing smoking or encouraging cessation. Special considerations should include assessment of level of nicotine dependence, which is associated with difficulty in quitting and relapse.

5. Coronary heart disease screening and treatment

Recommendations

Screening

- In asymptomatic patients, evaluate risk factors to stratify patients by 10-year risk, and treat risk factors accordingly.

Treatment

- In patients with known CVD, ACE inhibitor, aspirin, and statin therapy (if not contraindicated) should be used to reduce the risk of cardiovascular events.
- In patients with a prior MI, β-blockers should be continued for at least 2 years after the event.
- Longer-term use of β-blockers in the absence of hypertension is reasonable if well tolerated, but data are lacking.
- Avoid thiazolidinedione (TZD) treatment in patients with symptomatic heart failure.

- Metformin may be used in patients with stable CHF if renal function is normal. It should be avoided in unstable or hospitalized patients with CHF.

In all patients with diabetes, cardiovascular risk factors should be assessed at least annually. These risk factors include dyslipidemia, hypertension, smoking, a positive family history of premature coronary disease, and the presence of micro- or macroalbuminuria.

B. Nephropathy screening and treatment

Recommendations

General recommendations

- To reduce the risk or slow the progression of nephropathy, optimize glucose control.
- To reduce the risk or slow the progression of nephropathy, optimize blood pressure control.

Screening

- Perform an annual test to assess urine albumin excretion in type 1 diabetic patients with diabetes duration of 5 years and in all type 2 diabetic patients, starting at diagnosis.
- Measure serum creatinine at least annually in all adults with diabetes regardless of the degree of urine albumin excretion. The serum creatinine should be used to estimate GFR and stage the level of chronic kidney disease (CKD), if present.

Treatment

- In the treatment of the nonpregnant patient with micro- or macroalbuminuria, either ACE inhibitors or ARBs should be used.
- While there are no adequate head-to-head comparisons of ACE inhibitors and ARBs, there is clinical trial support for each of the following statements:

In patients with type 1 diabetes, hypertension, and any degree of albuminuria, ACE inhibitors have been shown to delay the progression of nephropathy.

In patients with type 2 diabetes, hypertension, and microalbuminuria, both ACE inhibitors and ARBs have been shown to delay the progression to macroalbuminuria.

In patients with type 2 diabetes, hypertension, macroalbuminuria, and renal insufficiency (serum creatinine >1.5 mg/dl), ARBs have been shown to delay the progression of nephropathy.

If one class is not tolerated, the other should be substituted.

- Reduction of protein intake to 0.8–1.0 g · kg body wt^{-1} · day^{-1} in individuals with diabetes and the earlier stages of CKD and to 0.8 g · kg body wt^{-1} · day^{-1} in the later stages of CKD may improve measures of renal function (urine albumin excretion rate and GFR) and is recommended.
- When ACE inhibitors, ARBs, or diuretics are used, monitor serum creatinine and potassium levels for the development of acute kidney disease and hyperkalemia.
- Continued monitoring of urine albumin excretion to assess both response to therapy and progression of disease is recommended.
- Consider referral to a physician experienced in the care of kidney disease when there is uncertainty about the etiology of kidney disease (active urine sediment, absence of retinopathy, or rapid decline in GFR), difficult management issues, or advanced kidney disease.

Diabetic nephropathy occurs in 20–40% of patients with diabetes and is the single leading cause of end-stage renal disease (ESRD). Persistent albuminuria in the range of 30–

299 mg/24 h (microalbuminuria) has been shown to be the earliest stage of diabetic nephropathy in type 1 diabetes and a marker for development of nephropathy in type 2 diabetes. Microalbuminuria is also a well-established marker of increased CVD risk. Patients with microalbuminuria who progress to macroalbuminuria (≥300 mg/24 h) are likely to progress to ESRD. However, a number of interventions have been demonstrated to reduce the risk and slow the progression of renal disease.

Intensive diabetes management with the goal of achieving near-normoglycemia has been shown in large prospective randomized studies to delay the onset of microalbuminuria and the progression of micro- to macroalbuminuria in patients with type 1 and type 2[103] diabetes.

Assessment of albuminuria status and renal function

Screening for microalbuminuria can be performed by measurement of the albumin-to-creatinine ratio in a random spot collection (preferred method); 24-h or timed collections are more burdensome and add little to prediction or accuracy. Measurement of a spot urine for albumin only, whether by immunoassay or by using a dipstick test specific for microalbumin, without simultaneously measuring urine creatinine, is somewhat less expensive but susceptible to false-negative and -positive determinations as a result of variation in urine concentration due to hydration and other factors.

Definitions of abnormalities in albumin excretion

Category	Spot collection (μg/mg creatinine)
Normal	<30
Microalbuminuria	30–299
Macroalbuminuria (clinical)	≥300

C. Retinopathy screening and treatment

Recommendations

General recommendations

- To reduce the risk or slow the progression of retinopathy, optimize glycemic control.
- To reduce the risk or slow the progression of retinopathy, optimize blood pressure control.

Screening

- Adults and children aged 10 years or older with type 1 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist within 5 years after the onset of diabetes.
- Patients with type 2 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist shortly after the diagnosis of diabetes.
- Subsequent examinations for type 1 and type 2 diabetic patients should be repeated annually by an ophthalmologist or optometrist. Less frequent exams (every 2–3 years) may be considered following one or more normal eye exams. Examinations will be required more frequently if retinopathy is progressing.
- High-quality fundus photographs can detect most clinically significant diabetic retinopathy. Interpretation of the images should be performed by a trained eye care provider. While retinal photography may serve as a screening tool for retinopathy, it is not a substitute for a comprehensive eye exam, which should be performed at least initially and at intervals thereafter as recommended by an eye care professional.
- Women with preexisting diabetes who are planning pregnancy or who have become pregnant should have a comprehensive eye examination and be counseled on the risk of development and/or progression of diabetic retinopathy. Eye examination should occur

in the first trimester with close follow-up throughout pregnancy and for 1 year postpartum.

Treatment

- Promptly refer patients with any level of macular edema, severe NPDR, or any PDR to an ophthalmologist who is knowledgeable and experienced in the management and treatment of diabetic retinopathy.
- Laser photocoagulation therapy is indicated to reduce the risk of vision loss in patients with high-risk PDR, clinically significant macular edema, and in some cases of severe NPDR.
- The presence of retinopathy is not a contraindication to aspirin therapy for cardioprotection, as this therapy does not increase the risk of retinal hemorrhage.

Diabetic retinopathy is a highly specific vascular complication of both type 1 and type 2 diabetes, with prevalence strongly related to duration of diabetes. Diabetic retinopathy is the most frequent cause of new cases of blindness among adults aged 20–74 years. Glaucoma, cataracts, and other disorders of the eye occur earlier and more frequently in people with diabetes.

In addition to duration of diabetes, other factors that increase the risk of, or are associated with, retinopathy include chronic hyperglycemia, the presence of nephropathy, and hypertension. Intensive diabetes management with the goal of achieving near normoglycemia has been shown in large prospective randomized studies to prevent and/or delay the onset and progression of diabetic retinopathy. Lowering blood pressure has been shown to decrease the progression of retinopathy.

One of the main motivations for screening for diabetic retinopathy is the established efficacy of laser photocoagulation surgery in preventing vision loss. Two large trials, the Diabetic Retinopathy Study (DRS) and the Early Treatment Diabetic Retinopathy Study (ETDRS), provide the strongest support for the therapeutic benefits of photocoagulation surgery.

Laser photocoagulation surgery in both trials was beneficial in reducing the risk of further vision loss, but generally not beneficial in reversing already diminished acuity.

Results of eye examinations should be documented and transmitted to the referring health care professional.

D. Neuropathy screening and treatment[104]

Recommendations

- All patients should be screened for distal symmetric polyneuropathy (DPN) at diagnosis and at least annually thereafter using simple clinical tests.
- Electrophysiological testing is rarely needed, except in situations where the clinical features are atypical.
- Screening for signs and symptoms of cardiovascular autonomic neuropathy should be instituted at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes. Special testing is rarely needed and may not affect management or outcomes.
- Medications for the relief of specific symptoms related to DPN and autonomic neuropathy are recommended, as they improve the quality of life of the patient.

The early recognition and appropriate management of neuropathy in the patient with diabetes is important for a number of reasons: *1*) nondiabetic neuropathies may be present in patients with diabetes and may be treatable; *2*) a number of treatment options exist for

symptomatic diabetic neuropathy; *3*) up to 50% of DPN may be asymptomatic, and patients are at risk of insensate injury to their feet; *4*) autonomic neuropathy may involve every system in the body; and *5*) cardiovascular autonomic neuropathy causes substantial morbidity and mortality. Specific treatment for the underlying nerve damage is not currently available, other than improved glycemic control, which may slow progression but not reverse neuronal loss. Effective symptomatic treatments are available for some manifestations of DPN and autonomic neuropathy.

Patients with diabetes should be screened annually for DPN using tests such as pinprick sensation, vibration perception (using a 128-Hz tuning fork), 10-g monofilament pressure sensation at the distal plantar aspect of both great toes and metatarsal joints, and assessment of ankle reflexes. Combinations of more than one test have >87% sensitivity in detecting DPN. Loss of 10-g monofilament perception and reduced vibration perception predict foot ulcers.[104]

The symptoms and signs of autonomic dysfunction should be elicited carefully during the history and physical examination. Major clinical manifestations of diabetic autonomic neuropathy include resting tachycardia, exercise intolerance, orthostatic hypotension, constipation, gastroparesis, erectile dysfunction, sudomotor dysfunction, impaired neurovascular function, "brittle diabetes," and hypoglycemic autonomic failure.

Gastrointestinal neuropathies (e.g., esophageal enteropathy, gastroparesis, constipation, diarrhea, and fecal incontinence) are common, and any section of the gastrointestinal tract may be affected. Gastroparesis should be suspected in individuals with erratic glucose control or with upper gastrointestinal symptoms without other identified cause. Evaluation of solid-phase gastric emptying using double-isotope scintigraphy may be

done if symptoms are suggestive, but test results often correlate poorly with symptoms. Constipation is the most common lower-gastrointestinal symptom but can alternate with episodes of diarrhea.

Diabetic autonomic neuropathy is also associated with genitourinary tract disturbances. In men, diabetic autonomic neuropathy may cause erectile dysfunction and/or retrograde ejaculation. Evaluation of bladder dysfunction should be performed for individuals with diabetes who have recurrent urinary tract infections, pyelonephritis, incontinence, or a palpable bladder.

Foot care

Recommendations

- For all patients with diabetes, perform an annual comprehensive foot examination to identify risk factors predictive of ulcers and amputations. The foot examination should include inspection, assessment of foot pulses, and testing for loss of protective sensation (LOPS) (10-g monofilament plus testing any one of: vibration using 128-Hz tuning fork, pinprick sensation, ankle reflexes, or vibration perception threshold).
- Provide general foot self-care education to all patients with diabetes.
- A multidisciplinary approach is recommended for individuals with foot ulcers and high-risk feet, especially those with a history of prior ulcer or amputation.
- Refer patients who smoke, have LOPS and structural abnormalities, or have history of prior lower-extremity complications to foot care specialists for ongoing preventive care and life-long surveillance.

- Initial screening for peripheral arterial disease (PAD) should include a history for claudication and an assessment of the pedal pulses. Consider obtaining an ankle-brachial index (ABI), as many patients with PAD are asymptomatic.
- Refer patients with significant claudication or a positive ABI for further vascular assessment and consider exercise, medications, and surgical options.

Amputation and foot ulceration, consequences of diabetic neuropathy and/or PAD, are common and major causes of morbidity and disability in people with diabetes. Early recognition and management of risk factors can prevent or delay adverse outcomes.

The risk of ulcers or amputations is increased in people who have the following risk factors:

- previous amputation
- past foot ulcer history
- peripheral neuropathy
- foot deformity
- peripheral vascular disease
- visual impairment
- diabetic nephropathy (especially patients on dialysis)
- poor glycemic control
- cigarette smoking

Many studies have been published proposing a range of tests that might usefully identify patients at risk of foot ulceration, creating confusion among practitioners as to which screening tests should be adopted in clinical practice. An ADA task force was therefore assembled in 2008 [105] to concisely summarize recent literature in this area and

recommend what should be included in the comprehensive foot exam for adult patients with diabetes. They recommend that at least annually, all adults with diabetes should undergo a comprehensive foot examination to identify high-risk conditions.

Patients with diabetes and high-risk foot conditions should be educated regarding their risk factors and appropriate management. Patients with visual difficulties, physical constraints preventing movement, or cognitive problems that impair their ability to assess the condition of the foot and to institute appropriate responses will need other people, such as family members, to assist in their care.

Foot ulcers and wound care may require care by a podiatrist, orthopedic or vascular surgeon, or rehabilitation specialist experienced in the management of individuals with diabetes

DIABETES CARE IN SPECIFIC POPULATIONS

A. Children and adolescents

Type 2 diabetes

The incidence of type 2 diabetes in adolescents is increasing, especially in ethnic minority populations. Distinction between type 1 and type 2 diabetes in children can be difficult, since the prevalence of overweight in children continues to rise and since autoantigens and ketosis may be present in a substantial number of patients with features of type 2 diabetes (including obesity and acanthosis nigricans). Such a distinction at the time of diagnosis is critical because treatment regimens, educational approaches, and dietary counsel will differ markedly between the two diagnoses.

Type 2 diabetes has a significant incidence of co morbidities already present at the time of diagnosis.[106] It is recommended that blood pressure measurement, a fasting lipid

profile, microalbuminuria assessment, and dilated eye examination be performed at the time of diagnosis. Additional problems that may need to be addressed include polycystic ovary disease and the various co morbidities associated with pediatric obesity such as sleep apnea, hepatic steatosis, orthopedic complications, and psychosocial concerns.

B. Preconception care

Recommendations

- A1C levels should be as close to normal as possible (<7%) in an individual patient before conception is attempted.
- Starting at puberty, preconception counseling should be incorporated in the routine diabetes clinic visit for all women of child-bearing potential.
- Women with diabetes who are contemplating pregnancy should be evaluated and, if indicated, treated for diabetic retinopathy, nephropathy, neuropathy, and CVD.
- Medications used by such women should be evaluated prior to conception because drugs commonly used to treat diabetes and its complications may be contraindicated or not recommended in pregnancy, including statins, ACE inhibitors, ARBs, and most noninsulin therapies.

Major congenital malformations remain the leading cause of mortality and serious morbidity in infants of mothers with type 1 or type 2 diabetes. Observational studies indicate that the risk of malformations increases continuously with increasing maternal glycemia during the first 6–8 weeks of gestation, as defined by first-trimester A1C concentrations. There is no threshold for A1C values below which risk disappears entirely. However, malformation rates above the 1–2% background rate of nondiabetic pregnancies appear to be

limited to pregnancies in which first-trimester A1C concentrations are >1% above the normal range for a nondiabetic pregnant woman.

Preconception care of diabetes appears to reduce the risk of congenital malformations. Studies have shown that, it is impossible to be certain that the lower malformation rates result from improved diabetes care. Nonetheless, the evidence supports the concept that malformations can be reduced or prevented by careful management of diabetes before pregnancy.

Planned pregnancies greatly facilitate preconception diabetes care. Unfortunately, nearly two-thirds of pregnancies in women with diabetes are unplanned, leading to a persistent excess of malformations in infants of diabetic mothers. To minimize the occurrence of these devastating malformations, standard care for all women with diabetes who have child-bearing potential, beginning at the onset of puberty or at diagnosis, should include *1*) education about the risk of malformations associated with unplanned pregnancies and poor metabolic control; and *2*) use of effective contraception at all times, unless the patient has good metabolic control and is actively trying to conceive.

Women contemplating pregnancy need to be seen frequently by a multidisciplinary team experienced in the management of diabetes before and during pregnancy. The goals of preconception care are to *1*) involve and empower the patient in the management of her diabetes, *2*) achieve the lowest A1C test results possible without excessive hypoglycemia, *3*) assure effective contraception until stable and acceptable glycemia is achieved, and *4*) identify, evaluate, and treat long-term diabetes complications such as retinopathy, nephropathy, neuropathy, hypertension, and CHD.[107]

Among the drugs commonly used in the treatment of patients with diabetes, a number may be relatively or absolutely contraindicated during pregnancy. Statins are category X (contraindicated for use in pregnancy) and should be discontinued before conception. Among the oral antidiabetic agents, metformin and acarbose are classified as category B (no evidence of risk in humans) and all others as category C. Potential risks and benefits of oral antidiabetic agents in the preconception period must be carefully weighed, recognizing that data are insufficient to establish the safety of these agents in pregnancy.

C. Older adults

Recommendations

- Older adults who are functional, are cognitively intact, and have significant life expectancy should receive diabetes care using goals developed for younger adults.
- Glycemic goals for older adults not meeting the above criteria may be relaxed using individual criteria, but hyperglycemia leading to symptoms or risk of acute hyperglycemic complications should be avoided in all patients.
- Other cardiovascular risk factors should be treated in older adults with consideration of the time frame of benefit and the individual patient. Treatment of hypertension is indicated in virtually all older adults, and lipid and aspirin therapy may benefit those with life expectancy at least equal to the time frame of primary or secondary prevention trials.
- Screening for diabetes complications should be individualized in older adults, but particular attention should be paid to complications that would lead to functional impairment.

Diabetes is an important health condition for the aging population; at least 20% of patients over the age of 65 years have diabetes, and this number can be expected to grow

rapidly in the coming decades. Older individuals with diabetes have higher rates of premature death, functional disability, and coexisting illnesses such as hypertension, CHD, and stroke than those without diabetes. Older adults with diabetes are also at greater risk than other older adults for several common geriatric syndromes, such as polypharmacy, depression, cognitive impairment, urinary incontinence, injurious falls, and persistent pain.

The American Geriatric Society's guidelines for improving the care of the older person with diabetes[43] have influenced the following discussion and recommendations. The care of older adults with diabetes is complicated by their clinical and functional heterogeneity. Some older individuals developed diabetes years earlier and may have significant complications; others who are newly diagnosed may have had years of undiagnosed diabetes with resultant complications or may have few complications from the disease. Some older adults with diabetes are frail and have other underlying chronic conditions, substantial diabetes-related comorbidity, or limited physical or cognitive functioning. Other older individuals with diabetes have little comorbidity and are active. Life expectancies are highly variable for this population but often longer than clinicians realize. Providers caring for older adults with diabetes must take this heterogeneity into consideration when setting and prioritizing treatment goals.

There are few long-term studies in older adults that demonstrate the benefits of intensive glycemic, blood pressure, and lipid control. Patients who can be expected to live long enough to reap the benefits of long-term intensive diabetes management and who are active, have good cognitive function, and are willing should be provided with the needed education and skills to do so and be treated using the goals for younger adults with diabetes.

For patients with advanced diabetes complications, life-limiting comorbid illness, or substantial cognitive or functional impairment, it is reasonable to set less-intensive glycemic target goals. These patients are less likely to benefit from reducing the risk of microvascular complications and more likely to suffer serious adverse effects from hypoglycemia. However, patients with poorly controlled diabetes may be subject to acute complications of diabetes, including dehydration, poor wound healing, and hyperglycemic hyperosmolar coma. Glycemic goals at a minimum should avoid these consequences.

Although control of hyperglycemia may be important in older individuals with diabetes, greater reductions in morbidity and mortality may result from control of other cardiovascular risk factors rather than from tight glycemic control alone. Special care is required in prescribing and monitoring pharmacologic therapy in older adults. Metformin is often contraindicated because of renal insufficiency or significant heart failure. TZDs can cause fluid retention, which may exacerbate or lead to heart failure. They are contraindicated in patients with CHF and if used at all should be used very cautiously in those with, or at risk for, milder degrees of CHF. Sulfonylureas, other insulin secretagogues, and insulin can cause hypoglycemia. Insulin use requires that patients or caregivers have good visual and motor skills and cognitive ability. Drugs should be started at the lowest dose and titrated up gradually until targets are reached or side effects develop.

Screening for diabetes complications in older adults also should be individualized. Particular attention should be paid to complications that can develop over short periods of time and/or that would significantly impair functional status, such as vision and lower-extremity complications.

D. Cystic fibrosis–related diabetes

Cystic fibrosis-related diabetes (CFRD) is the most common co morbidity in people with cystic fibrosis, occurring in 20% of adolescents and 40–50% of adults. The additional diagnosis of diabetes in this population is associated with worse nutritional status, more severe inflammatory lung disease, and greater mortality from respiratory failure. For reasons that are not well understood, women with CFRD are particularly vulnerable to excess morbidity and mortality. Insulin insufficiency related to partial fibrotic destruction of the islet mass is the primary defect in CFRD. Genetically determined function of the remaining β-cells and insulin resistance associated with infection and inflammation may also play a role. Encouraging new data suggest that early detection and aggressive insulin therapy have narrowed the gap in mortality between cystic fibrosis patients with and without diabetes and have eliminated the sex difference in mortality.

STRATEGIES FOR IMPROVING DIABETES CARE

The implementation of the standards of care for diabetes has been suboptimal in most clinical settings. A recent report[108] Indicated that only 57.1% of adults with diagnosed diabetes achieved an A1C of <7%, only 45.5% had a blood pressure <130/80 mmHg, and just 46.5% had a total cholesterol <200 mg/dl. Most distressing was that only 12.2% of people with diabetes achieved all three treatment goals.

While numerous interventions to improve adherence to the recommended standards have been implemented, the challenge of providing uniformly effective diabetes care has thus far defied a simple solution. A major contributor to suboptimal care is a delivery system that too often is fragmented, lacks clinical information capabilities, often duplicates services, and is poorly designed for the delivery of chronic care. The chronic care model (CCM)

includes five core elements for the provision of optimal care of patients with chronic disease: delivery system design, self-management support, decision support, clinical information systems, and community resources and policies. Redefinition of the roles of the clinic staff and promoting self-management on the part of the patient are fundamental to the successful implementation of the CCM. Collaborative, multidisciplinary teams are best suited to provide such care for people with chronic conditions like diabetes and to empower patients' performance of appropriate self-management. Alterations in reimbursement that reward the provision of quality care, as defined by the attainment of quality measures developed by such programs as the ADA/National Committee for Quality Assurance Diabetes Provider Recognition Program, will also be required to achieve desired outcome goals.

In recent years, numerous health care organizations, ranging from large health care systems such as the U.S. Veteran's Administration to small private practices, have implemented strategies to improve diabetes care. Successful programs have published results showing improvement in process measures such as measurement of A1C, lipids, and blood pressure. Effects on important intermediate outcomes, such as mean A1C for populations, have been more difficult to demonstrate.[109] Features of successful programs reported in the literature include

- Delivery of DSME: increases adherence to standard of care and educating patients on glycemic targets and improves the percentage of patients who reach goal A1C
- Adoption of practice guidelines, with participation of health care professionals in the process of development: Guidelines should be readily accessible at the point of service, preferably as computerized reminders at the point of care. Guidelines should begin with

a summary of their major recommendations instructing health care professionals what to do and how to do it.

- Use of checklists that mirror guidelines: successful at improving adherence to standards of care
- Systems changes: such as provision of automated reminders to health care professionals and patients and audit and feedback of process and outcome data to providers
- Quality improvement programs combining continuous quality improvement or other cycles of analysis and intervention with provider performance data
- Practice changes: such as availability of point of care testing of A1C, scheduling planned diabetes visits, clustering of dedicated diabetes visits into specific times within a primary care practice schedule, or group visits and/or visits with multiple health care professionals on a single day

Tracking systems with either an electronic medical record or patient registry: helpful at increasing adherence to standards of care by prospectively identifying those requiring assessments and/or treatment modifications. They likely could have greater efficacy if they suggested specific therapeutic interventions to be considered for a particular patient at a particular point in time.[110]

Availability of case or (preferably) care management services: Nurses, pharmacists, and other nonphysician health care professionals using detailed algorithms working under the supervision of physicians have demonstrated the greatest reduction in A1C and blood pressure.[111]

Evidence suggests that these individual initiatives work best when provided as components of a multifactorial intervention. When practices are compared, those that

address more of the CCM elements demonstrate lower A1C levels and lower cardiovascular risk scores. The most successful practices have an institutional priority for quality of care, involve all of the staff in their initiatives, redesign their delivery system, activate and educate their patients, and use electronic health record tools.

It is clear that optimal diabetes management requires an organized, systematic approach and involvement of a coordinated team of dedicated health care professionals working in an environment where quality care is a priority.

DIABETES AND CARCINOMA

Recent studies conducted in India and Hungary show an increased prevalence of premalignant lesions among diabetic patients. The oral epithelium provides a normal protective barrier against carcinogens. In diabetic patients, progressive atrophy of oral mucosa occurs due to a decreased rate of salivary secretion and low salivary pH, increasing the possibility of lesions such as glossitis and cheilitis. In theory, loss of the normal protective barrier can increase the permeability of the oral mucosa to carcinogens. Studies have suggested an increased prevalence of premalignant lesions such as leukoplakia, in diabetic (type 2) patients but is not supported by definitive histopathologic diagnosis. The studies also lack information about whether the occurrence of diabetes was prior or the premalignant lesion. Components of betel quid can affect cell mediated immunity. In diabetic patients, T – cell function as well as the cellular immune response is impaired. Thus diminished immunity in diabetic patients may facilitate the action of carcinogens. In addition, there can be microangiopathy in the gingival tissues causing tissue hypoxia and a reduced blood supply, which together with the impaired cellular immune response may play a role in the development of oral cancer.[112]

An association between diabetes mellitus and alterations in the oral mucosa has been observed in experimental studies and clinical practice, and includes changes in the healing process of lesions as well as the triggering infectious processes in the mucosal lining.[113] Microscopic examination of mice with confirmed diabetes showed atrophy of the oral epithelium, with clear cellular pleomorphism and poorly defined cell layers. The alterations seen include reduced number of cell orgennels, cell membrane disorganization, the accumulation of lipid droplets in the cytoplasm, increased intercellular space and slight superficial desquamation.[114]

Our study [115] on cytomorphometric analysis and assessment of periodic Acid Schiff positivity of exfoliated cells from apparently normal buccal mucosa of type 2 diabetic patients showed a significantly higher nuclear area in the exfoliated cells of diabetic patients as compared to non diabetic group. The increase in the nuclear area could be due to a delay in the keratinisation process caused by decreased cellular turnover. In diabetics the Glycation of proteins, lipids and nucleic acids increases with sustained hyperglycemia, causing much greater accumulation of advanced Glycation end products in the walls of large vessels as well as in the basement membrane of microvasculature.this effects progressive narrowing of the vessel lume, decreased perfusion of affected tissues and a decrease in turnover which may cause a delay in the differentiation process of the epithelium leading to increase in the cells which present a large nucleus as primary characteristic.

Oxidative stress is defined as a persistent imbalance between the production of highly reactive molecular species (chiefly oxygen and nitrogen) and antioxidant defenses, leading to tissue damage.[116]

Oxidative stress results from increased content of reactive oxygen species (ROS) and or reactive nitrogen species (RNS). Examples of ROS include charged species such as superoxide and the hydroxylradical, and uncharged species such as hydrogen peroxide.

There are data indicating that ROS formation is a direct consequence of hyperglycemia. More recent studies have suggested that increased FFA levels may also result in ROS formation.

Because of their ability to directly oxidize and damage DNA, protein and lipid, ROS are believed to play a key direct role in the pathogenesis of late diabetic complications. In addition to their ability to directly inflict macromelecular damage, ROS can function as signaling molecules to activate a number of cellular stress – sensitive pathways that cause cellular damage and are ultimately responsible for the late complications of diabetic.

Furthermore, these same pathways are linked to insulin resistance and decreased insulin secretion.

In this review it is proposed that ROS and oxidative stress induced by elevations in glucose and possibly FFA levels play a key role in causing insulin resistance and β cell dysfunction by their ability to active stress sensitive signaling pathways.

Research in numerous laboratories has indicated that hyperglycemia activates several major, well characterized biochemical pathways that play a significant role in the etiology of diabetic complications. These pathways include advanced glycation end products (AGE's) and receptors for AGE (RAGE), protein kinases c (PKC) and the polyol pathway.

More recently, hyperglycemia has been implicated in the activation of additional biochemical pathways including the stress –activated signaling pathways of nuclear factor –

KB (NF-KB), NH2 terminal junkinases / stress actvated protein kinases (JNK / SAPK), p38 nitrogen activated protein (MAP) kinase, and hexosamine.

NF-KB pathway

Plays a critical role in mediating immune and inflammatory response and apoptosis. NF-KB regulates expression of a large number of genese, including several of those linked to the complications of diabetes (Eg VEGF). Many of these gene products regulated by NFKB in turn activate NF-KB leading to a vicious circle.

JNK/SAPK pathway

The JNK/SAPKs are members of the complex superfamily of MAP serine / threonine protein kinases. This super family also includes the P33 MAP kinases (p38 MAPKs) and the extracellular signal related kinases (ERKs).

In contrast to ERK's which are typically activated by mitogens, JNK/SAPK are P38 MAPK are known as stress activated kinases and are responsive to a variety of exogenous and endogenous stress inducing stimuli, including hyperglycemia, ROS< oxidative stress, osmotic stress, proinflammatory cytokines, heat shock and ultraviolet irradiation.

JNK / SAPK are activated by hyperglycemia induced oxidative stress and are likely involved in apoptosis mediated by hyperglycemia in human endothelial cell.

P38 MAPK pathway

Activation of this pathway occurs in response to hyperglysemia and in diabetes. The effects on P38 MAPK are known to be mediated by increased ROS production. Increases in this pathway have been noted in nerve tissue of patients with type 1 and type2 diabetes although the causative role in the pathophysiology has not been established.

Hexosaamine pathway:

Increase glucose flux or FFA into variety of cell types results in the activation of Herosamine pathway, which inturn leads to insulin resistance and development of late diabetic complications.

Taken together, there is a strong evidence to indicate that NFKB, JNK/SAPK, P38 MAOK and hexosamine pathways are stress sensitive signaling systems that can be activated by hyperglycemia and ROS in vitro and in vivo. Chronic activation of these pathways is associated with a late complications of diabetes.

Oxidative stress and insulin resistance

In type 2 diabetes insulin resistance most often precedes the onset of disease by many years and is also multifactorial. It is clear that insulin resistance has a genetic component. Insulin resistance is a feature of the off spring of parents with type 2 diabetes, aggregates in families and in longitudinal studies of families has been implicated as a major risk factor for developing type 2 diabetes.

Insulin resistance is also caused by acquired factors such as obesity, sedentary life style, pregnancy and presence of excess hormones. Initially, insulin resistance is compensated by hyperinsulinemia, through which normal glucose tolerance is preserved. It has been reported that at least 25% of non diabetic individuals exhibit insulin resistance that is in range which will be seen in diabetic patients. Deterioration in to impaired glucose tolerance occurs when either the insulin resistance increases or the compensatory insulin secretory response decrease, or when both occur. An increase in insulin, FFA and or glucose levels can increase ROS production and oxidative stress as well as activate stress sensitive

pathways. This inturn can worsen both insulin action and secreation, there by accelerating the progression towards overt type 2 diabetes.

Oxidative stress and β-cell dysfunction

β-cells are responsible for sensing and secreting the appropriate amount of insulin in response to a glucose stimulus. This process is complex and dependent on many factors. The critical importance of mitochondrial glucose metabolism in linking stimulus to secretion is well established. Therefore the ability of oxidative stress (H_2O_2) to damage mitochondria and markedly blunt insulin secretion is not surprising.

Many studies have suggested that β-cell dysfunction is the result of prolonged exposure to high glucose, elevated FFA levels or a combination of two.

B-cells are sensitive to ROS and RNS because they are low in free radical quenching (antioxidant) enzymes such as catalase, glutathione peroxidase and superoxide dismutase.

Oxygen stress generated by short exposure of β-cell preparations to H_2O_2 increases production of P21, decreases insulin mRNA, cytosolic ATP and calcium flux in cytosol and mitochondria and causes apoptosis. β-cell glucose induced toxicity, β-cell lipid induced toxicity, β-cell combined glucose / lipid toxicity.

Conclusion

Hyperglycemia and possibly elevated FFA levels results in the generation of ROS and RNS and consequently increased oxidative stress. In the absence of an appropriate compensatory response from the cells endogenous antioxidant network, the system becomes overwhelmed, resulting in redox imbalance, thereby further exacerbating the situation. The reactive specieis not only directly damage cells by oxidizing DNA, protein and lipids but

indirectly by activating a variety of stress sensitive intracellar signaling pathways like NF-KB, P38 MAPK, JNK / SAPK, hexosamine, PKC, AGE / RAGE, sorbitol and others.

Activation of these pathways results in increased expression of numerous gene products that also cause cellular damage and play a major role in the etiology of late complications of diabetes.

Work to be done in future

1. Screening tests to monitor oxidative stress need to be standardized and used in patients with diabetes.
2. Antioxidants either olderones like vitamin E, LA and NAC need to be reformulated or else newer antioxidants needs to be improved.
3. Strategies to interrupt the stress pathways needs to be studies more thoroughly
4. Additional research is needed to firmly establish weather either the reduction of ROS formation activated by hyperglycemia and elevated FFA levels and or the block age of the ROS induced stress pathways will result in improved insulin action and or secretion.

Saliva: [117]

The glands of the mouth are called salivary glands, and the composite of their secretion is termed saliva. The glands which produce saliva include three major paired glands the Parotid, submandibular and sublingual glands along with several hundred smaller minor or accessory salivary glands scattered on the inner surface of the lips and cheeks, over the hard and soft palates and on the surface of the tongue. Their secretion with the exception of those on the tongue around cicumvallate papillae, is predominantly mucous i.e. rich in mucoproteins and their main function is lubrication, although they also secrete

immunoglobulin's and other proteins. Those below circumvallate papillae are called glands of Von Ebner, and they secrete a watery secretion whose purpose is to solubilise substances to give them the possibility of stimulating the taste cells around the papillae. It is likely that the minor salivary glands are continuously active and there is evidence that the usual stimuli to secretion which affect the minor salivary glands have little effect on the minor glands. The submandibular and sublingual glands also secrete continuously at low level, but can increase this 10-20 times when stimulated appropriately. The parotid glands have no measurable unstimulated secretion in most individuals but become the major source of saliva when stimulated.

The saliva collected by dribbling or spitting variously termed whole saliva or mixed saliva or more precisely oral fluid is termed as unstimulated saliva which varies in composition than that collected from particular glands on stimulation is termed stimulated saliva. Thus, an unstimulated whole saliva is dominated by the submandibular components, while an stimulated saliva has a composition much closer to that of parotid saliva.

Structure of the secretory unit

A section through a typical salivary gland shows a bewildering mixture of cells, some clearly arranged in a circle with a central space, others apparently forming small islands and, in some glands, still others capping the islands of cells. If one could view such a section in three dimensions, one would see epithelial cells forming the walls of ducts, arranged as spherical aggregations in the acini, and forming minor components on the surface of these spherical structures. The excretory duct of salivary glands is in continuity with the oral mucosa: it is lined with a stratified squamous epithelium. As one passes into the gland this duct divides into main branches, the lobular ducts, lined

with a columnar epithelium and these in turn continue to divide into smaller and smaller branches. The epithelium remains columnar as the ducts decrease in size but becomes striated in appearance because of extensive invaginations in the base of the cells. These striated ducts give way to the cuboidal cell walled intercalated ducts and finally reach a blind end in the acinus with its surrounding secretory cells. In glands such as the submandibular which contain both mucous and serous cells, the mucous cells usually form the acinus and the flattened (semilunar) serous cells surround the mucous cells .The striated ducts are present in the parotid and submandibular glands but absent from the sublingual and many of the minor salivary glands. Myoepithelial cells with a central nucleus and long processes extending round the acinus or sometimes the duct are termed basket cells because of this morphological appearance. The acinar cells are of two types when stained for optical microscopy: the basophilic serous cells with their secretory granules and the eosinophilic mucous cells with their pale-staining vacuoles containing mucoproteins. The serous cell has a basally situated nucleus, an extensive endoplasmic reticulum, well-developed Golgi apparatus and numerous granules passing to the acinar surface for exocytosis. The mucous cell is almost filled with vacuoles of secretory material; the nucleus is crushed towards the base of the cell, the Golgi apparatus lies more apically and the rough endoplasmic reticulum is basal and between the vacuoles. The intercalated duct is short and its cells appear relatively unspecialized. One of the functions of these cells may be to act as progenitors for the acinar cells but they do also seem to have some secretory functions.

The cells of the striated ducts are concerned with the modification of the saliva initially formed in the acini. They have extensively infolded basal membranes, many

mitochondria and intense sodium-potassium-ATPase activity basally. These features are typical of cells engaged in unidirectional transport of ions.

The blood supply to the major salivary glands

The blood circulation to the glands is important in saliva production. There is some interesting research which suggests that the pressure produced by the secretion of saliva - the pressure driving saliva along the ducts and out into the mouth - depends upon the arterial blood pressure within the gland. Stimulation of the parasympathetic supply to the salivary glands results in an increased blood flow to them. The blood supply, like that of the kidney, is thought to be a portal one - that is, one where two capillary systems are in series. The arterioles break up into a capillary bed around the ducts, the capillaries recombine and then a second set of capillaries are formed around the acini. Thus the reabsorption of ions around the ducts is balanced by the transfer of ions to the secretory epithelium of the acini. It is equally possible that the two capillary systems are arranged the other way round, with the acinar capillaries first and the ductal second. However, the histological appearance of the glands makes it difficult to tell which of these arrangements is correct and the lack of separation of ductal and acinar portions of the gland may mean that such a dual system is unnecessary - a single capillary bed could serve both acini and ducts.

The nerve supply to the major salivary glands

The main control of the salivary glands is through the parasympathetic nerves. Although these originate in the salivatory nuclei they synapse in ganglia near or in the glands and the final efferent fibres are short. The neurotransmitter in the ganglia is acetylcholine and the receptors are nicotinic; the neurotransmitter at the cells of the gland is also acetylcholine but the receptors on the acinar cells are muscarinic. It is possible that other transmitters in addition to acetylcholine can be released from the varicosities of the

parasympathetic nerve fibres (parasympathetic nerves usually provide an en passant innervations rather than a multitude of nerve terminals) and experiments in animals have demonstrated receptors for a number of neuro peptides such as substance P. It is not clear how important these are in humans although some of the atropine resistant effects of parasympathetic stimulation may be due to these. The parasympathetic fibres to the submandibular and sublingual glands pass in the facial nerve to the inner ear and then in its chorda tympani branch to the submandibular ganglion .The efferent supply to the parotid gland travel in the glossopharyngeal nerve to the otic ganglion and thence to the gland. The sympathetic fibres pass from the second thoracic segment of the spinal cord to the superior cervical ganglion on each side and the postganglionic fibres travel with blood vessels to the glands. The neurotransmitter in the ganglion is acetylcholine, whilst that at the acinar cells is noradrenaline: the adrenoreceptors there are both alpha-1 and beta-2 in their responses. The glands do not solely consist of acini: they have ductal systems which modify the initial secretion, myoepithelial cells which may assist in the expulsion of saliva from the gland, and blood vessels which supply nutrients, metabolic subtrates, water and ions necessary for secretion to occur. Even the secretory cells are of two types, one type described as mucous and secreting mucoproteins, and the other, described as serous, producing a less viscous secretion with amylase and proline-rich proteins as the main organic constituents. There is no direct evidence to suggest that the innervation of the serous and mucous cells is different, but it is possible that the distribution and sensitivity of receptors on the cells may differ and provide selective responses. Cholinesterase activity has been demonstrated in or close to ductal cells, suggesting that they may have a parasympathetic innervation. The innervation of the myoepithelial cells is uncertain; in animal experiments they have been shown to respond to neurotransmitters of both the sympathetic and parasympathetic systems and also to bradykinin. There is continuing debate as to the role and importance of these cells. The

blood vessels of the salivary glands are, like blood vessels elsewhere in the body, subject to parasympathetic control and stimulation of the parasympathetic supply leads to activation of alpha receptors and a vasoconstriction. However, these blood vessels also have a parasympathetic nerve supply and respond to stimulation with vasodilatation - one of the very few instances of parasympathetic induced vasodilatation in the human body. The neurotransmitter involved is almost certainly not acetylcholine but is probably vasoactive intestinal peptide (VIP). Nitric oxide (NO) is another likely candidate, but this possibility has not as yet been explored. The difficulty of explaining how sympathetic stimulation can result in secretion when it simultaneously causes vasoconstriction has been overcome by the suggestion that kallikrein is one of the secretory products of the ductal cells and this can diffuse back into the extracellular space and generate bradykinin in the local circulation: bradykinin is a vasodilator associated with secretion in other glands in the body.

The process of secretion

The stimuli to digestive organs could occurr in three phases: cephalic, intraorgan and interorgan. As the mouth is a cephalic organ. The first phase includes a psychological phase - the thought of food - and the related visual phase - the sight of food - as well as the more direct olfactory stage - the smell of food. It has even been suggested that the sound of cooking of some foods may stimulate salivary flow. These stimuli are conditioned stimuli because they represent an association of the stimulus with actual food intake rather than the direct oral stimulus of food intake. There is still debate as to how far they increase salivary secretion: their effect, if any, is very small, and it may be that these stimuli lead to an enhanced awareness of saliva in the mouth rather than an actual increase in secretion.

The within-organ stimuli are the most important for salivary secretion. They include the mechanical stimuli - those involving touch or pressure on oral structures and movements

of the masticatory muscles and mandible - and those involving chemical substances which stimulate the taste receptors. The stimuli vary in their effects, with mechanical stimuli being least effective in producing a flow of saliva and acid-tasting substances being most effective. As the nasal cavity is continuous with the oral cavity, smell does affect the flavor of foods and so there is a possibility of a direct olfactory stimulus to secretion, but there is no evidence to support this. However, olfactory irritants can increase salivary flow, presumably by a direct rather than a conditioned reflex. Stimulation of taste, touch and muscle and joint proprioceptive receptors unilaterally stimulates secretion on the ipsilateral side of the mouth.

Stimuli to taste receptors innervated by the lingual nerve and chorda tympani result in a greater stimulation of the sublingual and submandibular glands which are innervated by efferent fibres in the same nerve, whilst stimuli to taste receptors innervated by the glossopharyngeal nerve are more effective in stimulating the glossopharyngeal-innervated parotid gland.

The output pathways of all the salivary reflexes are via nerves. Hormones are not involved in the control of salivary secretion, although circulating aldosterone can affect the composition. The major glands have a dual nerve supply from the sympathetic and parasympathetic divisions of the autonomic nervous system. The cell bodies of the secretomotor neurons in the parasympathetic system are in the peripheral ganglia close to the glands, but the preganglionic fibres have cell bodies grouped together in the reticular formation to form two salivatory centers, the superior related to the nucleus of the facial nerve and controlling the submandibular and sublingual glands, the inferior related to the nucleus of the glossopharyngeal nerve and controlling the parotid glands. Stimulation of

these centres induces salivation on the ipsilateral side. The preganglionic cell bodies in the sympathetic nervous system are located at the level of the second thoracic nerve. Cells in either system may receive inputs from the various receptors either directly or via inter neurons and may also be excited or inhibited by impulses from higher centers. These latter may form parts of the patterned reflexes in which certain stimuli generate stereotyped patterns of response integrated across several effector systems. Vomiting, with its preparatory stimulation of salivary flow, is an example of this. Stimulation of the cerebral cortex at the lower end of the fissure of Rolando and the junction of the frontal and anterior sigmoidal gyri, or stimulation of the rhinencephalon near the amygdaloid nucleus, can provoke a feeding reaction which includes increased flow of saliva. The hypothalamus exerts an overriding control as a higher centre: in addition to its direct connections with the sympathetic system it mediates the primitive reactions of fear, rage and excitement, which include both dryness of mouth and excess salivation in different circumstances. Salivation is normally inhibited or reduced during sleep - another central control. The progressive reduction in the unstimulated salivary flow rates of infants between birth and 5 years of age - a period when maturation of the brain and nervous responses is occurring - demonstrates the progressive increase in inhibitory signals from higher centers.

The formation of the initial acinar fluid

Parasympathetic stimulation results in the binding of acetylcholine to the muscarinic receptors on the acinar cells. This activates a G-protein pathway causing the activation of phospholipase C and the splitting of phosphatidylinositol 4,5-diphosphate to give inositol trisphosphate and diacylglycerol. Inositol trisphosphate (IP_3) stimulates calcium release from the calcium stores within the cell and this free ionised calcium passes through the cell

to give three effects. It causes the opening of basal potassium channels, the opening of apical chloride channels, and the movement of secretary granules or vesicles towards the apical membrane and their fusion with the membrane to begin the process of exocytosis. The opening of potassium channels results in outward diffusion of potassium ions. This can sometimes be detected as a very high concentration of potassium in the first few drops of saliva collected after stimulation. Basally it raises the concentration of potassium in the extracellular fluid and this activates a sodium-potassium-chloride transporter in the basal and basolateral cell membranes, carrying the three ions into the cell. The energy for this transport is derived from the sodium ion concentration gradient maintained by the basolateral and lateral sodium-potassium-ATPase pumps. The ions are carried as two potassium's and three chlorides for every sodium ion transported. The potassium replaces that lost through the potassium channels and the sodium is excreted from the cell by the sodium-potassium pumps. The increasing concentration of chloride ions results in their diffusion out through the apical, or acinar, cell membrane into the acinar space. Increasing concentrations of chloride in the acinar fluid drag sodium ions to balance the charge and water down an osmotic gradient, probably between the acinar cells despite their tight apical junctions. Protein and mucoprotein are exocytosed into the acinar space where the tight junctions prevent their diffusion away from the acinar fluid.

Sympathetic stimulation at alpha receptors activates the same pathway as acetylcholine, but at the beta-2 receptors a different second messenger system is invoked. Activation of the excitatory G-protein results in adenylyl cyclase activation and the production of cyclic adenosine monophosphate (cAMP). This in turn activates protein kinase A and also causes mobilisation of calcium ions. At least a proportion of the increase

in ionic calcium concentration results from opening of calcium channels permitting calcium to flow into the cells. There is a rapid opening of potassium channels and the process of fluid secretion is initiated. However, this is on a much smaller scale than that induced by the inositol trisphosphate pathway, and the major result of sympathetic stimulation is the secretion of protein and mucoprotein, giving a thick viscous saliva.

Both neurotransmitters, acetylcholine and noradrenaline, are broken down rapidly. Aacetylcholinesterease is present in the acinar cell membranes and the salivary glands contain high concentrations of monoamine oxidases.

There are other effects of stimulation on the acinar cells: the net inward movement of chloride brings in water down an osmotic gradient and the cells tend to swell, whilst the increased cell activity increases the cell acidity. The former activates stretch-sensitive calcium channels in the cell membrane and outward movement of calcium reduces the ionic excess in the cells. Cell buffering is achieved by outward pumping of hydrogen ions or by exchange of hydrogen carbonate and chloride ions.

It is not known whether stimulation by either pathway can cause synthesis of new protein for export or whether replenishment of protein stores is simply an ongoing process. Prolonged stimulation of the parotid gland results in a diminution in protein concentration of the secretion but in the short term like half an hour but the protein concentration remains remarkably steady at a given level of stimulation. The net result of these processes is the formation of an acinar, or initial, secretion which is roughly similar in ionic composition to interstitial fluid in sodium and chloride concentrations, but with slightly higher potassium and calcium concentrations. It also contains the exocytosed proteins, but large molecules such as these have little effect on the osmotic activity of the solution and so the initial saliva is virtually isotonic with plasma.

Ductal modification of the acinar secretion

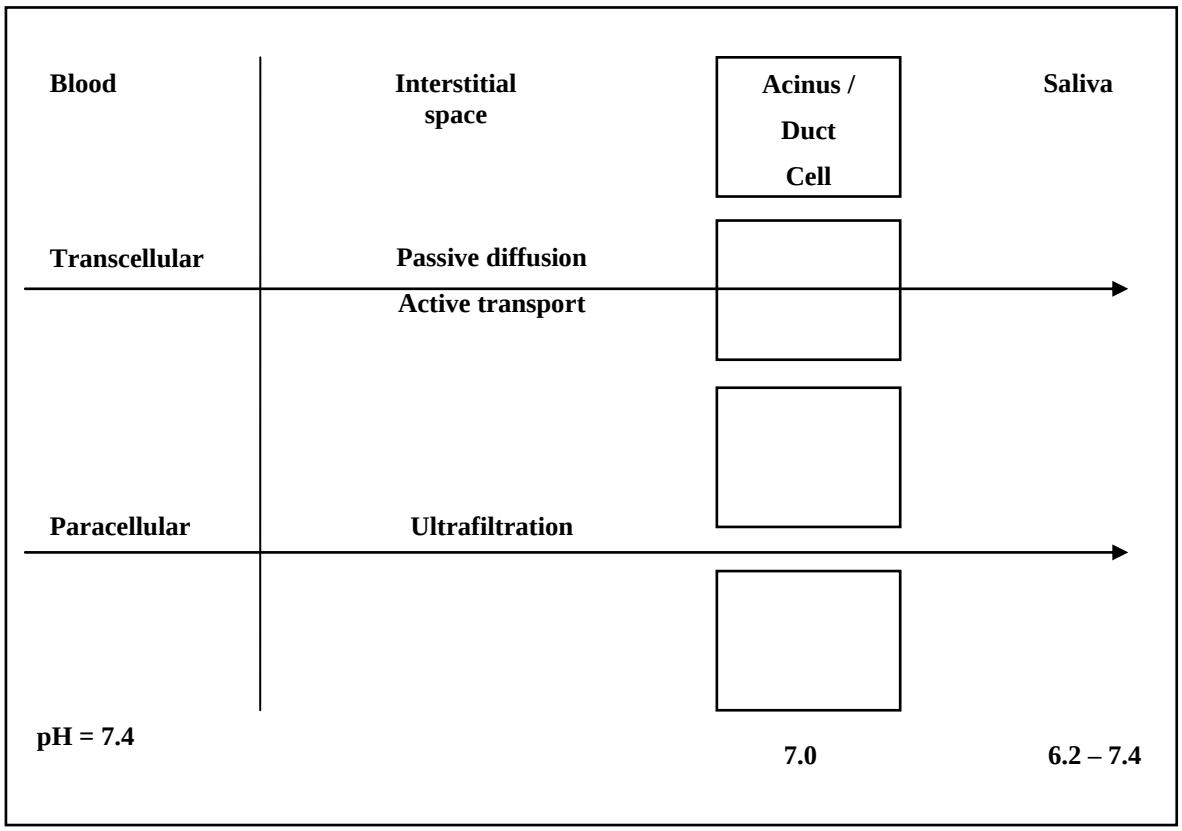
Saliva as secreted into the oral cavity is a hypotonic solution which varies in sodium concentrations from less than 10 mmol/I up to around 100 mmol/I. Chloride concentrations are similarly variable and below those in extracellular fluids generally, whilst hydrogen carbonate concentrations are usually in excess of those in extracellular fluids. These changes are accomplished within the ducts and, more particularly, in the striated ducts.

The intercalated ducts are short in humans and no specific functions have been identified for them. Nevertheless, it has been suggested that they can secrete proteins similar to those from the acinar cells. They do not contain any significant number of organelles which would normally be seen in secreting cells. In rodents there is another type of cell in this part of the ductal system: it contains many granules and hence the duct is described as the granular duct. It secretes kallikrein and a number of other proteolytic enzymes. It is possible that the human intercalated duct is the site of kallikrein secretion. A number of other proteins found in human saliva are secreted in the ductal system but the exact site of secretion has not been identified. In the case of secretory IgA, the immunoglobulin is synthesised in the lymphoid follicles dispersed throughout the glands and probably passes between the relatively loosely connected ductal cells. Lysozyme and lactoferrin are proteins of ductal origin, as is carbonic anhydrase. Serum albumin also reaches Saliva by intercellular diffusion in very small amounts, although the higher concentrations observed in whole saliva result from the mixing in the mouth with gingival fluid. The salivary amylase found in plasma passes across the ductal epithelium in the opposite direction, when a salivary duct is obstructed, the intra luminal pressure rises and the ductal epithelium becomes very leaky, plasma salivary amylase concentrations rise markedly when this happens.

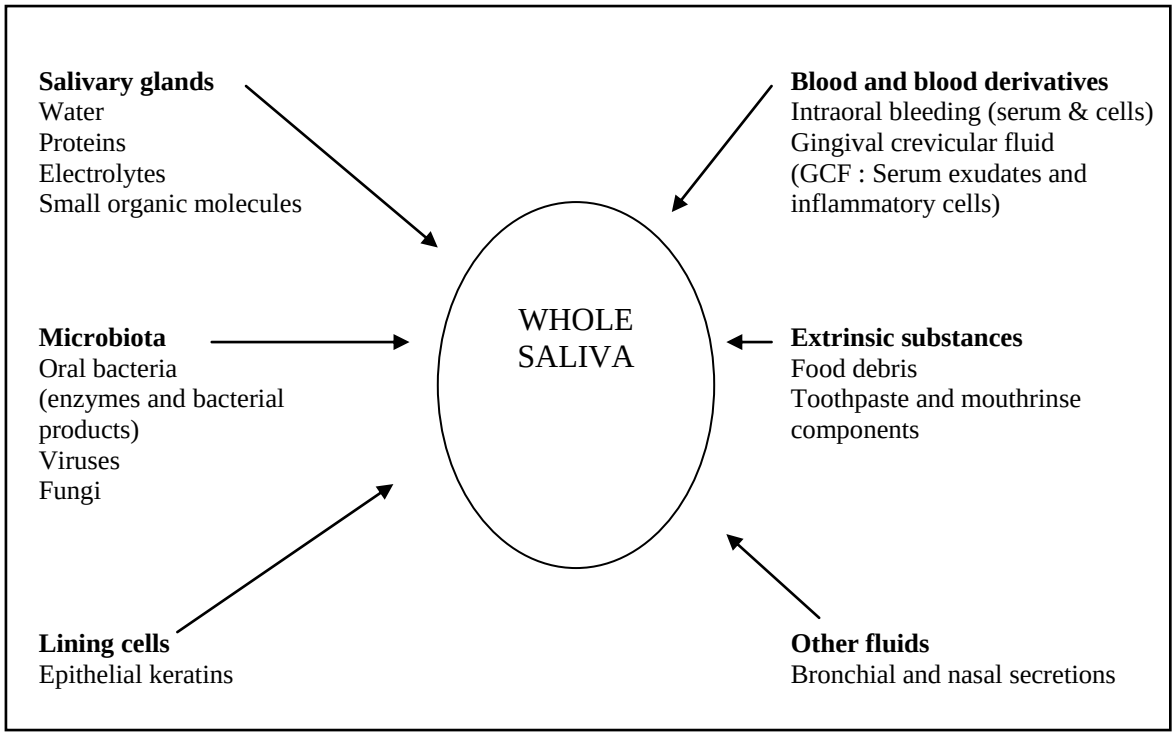
The striated ducts which are found in parotid and sub Mandibular glands are the main site of modification of ionic composition. They are said to be absent in sub lingual gland and monor salivary glands, but there is evidence that some labial glands may be able to produce a hypotonic saliva.

Sodium potassium pumps in the intercalated duct cells are found mainly on the infolded basal surface where the infoldings result in a greatly increased surface area. Activation of these pumps generates a concentration gradient across the cells and sodium passes from the luminal fluid into the cells and out across the basement membrane. This is similar to the process which takes place in proximal tubule of kidney. However the ductular cells differ from those of kidney, in being relatively impermeable to water so that the fluid in the proximal tubule remains isotonic and that in the striated duct becomes hypotonic. The duct is capable of almost reducing the sodium concentration to zero if the saliva stays in it for sufficiently longer period of time. Thus in very slow flowing saliva the concentration of sodium is less than 10mmol / l. The process of reabsorption is time dependent and hence sodium concentrations rise as saliva flow rate increases. Damage to ductal cells in any form will increase the sodium concentration in the saliva.

Throughout the ductal system addition of potassium ions to the ductal fluid takes place. Chloride ions are reabsorbed in the striated duct .In the remainder of the ductal system there is addition of potassium ions to the ductal fluid. The movements of water and ions take place across the salivary gland epithelium by the various processes as described. The ultimate source of water and ions in saliva is the blood plasma and the interstitial fluid derived from it.



Composition of saliva



The saliva is a mixture of secreations with substantial component from minor glands. Mixing of secreations takes place, but the fluid near the orifices of the ducts of the major glands will be nearer in composition to the appropriate secreation. During mastication when there is increased flow and effective volume of the mouth is available, the saliva is mixed with food.

The mixed secreations which are collected by expectoration are termed whole saliva or mixed saliva.Since these terms are not satisfactory the word oral fluid is used as better alternative. This terminology also avoids the implication that the expectorated fluid contains only the secretions of salivary glands. The fluid will contain contributions from gingival crevicular fluid, bacteria and white blood cells, and rarely food particles during and immediately after food intake.

Because of the availability of Lashley cannula or cup for easy collection of pure secreation, greater amount of information is available regarding parotid saliva. How ever whole saliva should give best assessment of the nature of oral environment.

Ionic composition: very 'leaky'; plasma salivary amylase concentrations rise markedly when this happens.

The striated ducts which are found in the parotid and submandibular glands are the main sites of modification of ionic composition. They are said to be absent in the sublingual and minor glands, but there is evidence that some labial glands may be able to produce a hypotonic saliva. Sodium-potassium pumps in the intercalated duct cells are found mainly on the infolded basal surface where the infoldings result in a greatly increased surface area. Activation of these pumps generates a concentration gradient across the cells and sodium passes from the luminal fluid into the cells and out across the basal membrane a process

very similar to that in the proximal tubules of the kidney. These cells differ from those of the kidney proximal tubule, however, in being relatively impermeable to water, so that the fluid in the proximal tubule remains isotonic and that in the striated duct becomes hypotonic. The duct is capable of reducing the sodium concentration almost to zero if the saliva stays in it for a sufficiently long period: in very slow flowing saliva the sodium concentrations are less than 10 mmol/1. The process of reabsorption is time-dependent and hence sodium concentrations rise as saliva flow rate increases. Damage to the ductal cells, such as may occur as a result of radiation, will increase the sodium concentrations in the saliva reaching the oral cavity.

Throughout the ductal system there is addition of potassium ions to the ductal fluid but, as in the kidney, the removal of sodium in the striated duct does not have a major role in this, probably because the accompanying movement of chloride ions balances the charge difference. Chloride ions are reabsorbed in the striated duct by two mechanisms: the transport gives a charge gradient for anions, and the presence of chloride-hydrogen-carbonate exchange proteins in the apical cell membranes allows chloride to pass into the cells and hydrogen carbonate to pass out. It is in this part of the duct, therefore, that chloride concentrations fall and hydrogen carbonate concentrations rise.

In the remainder of the ductal system there may be some addition of potassium ions to the ductal fluid; whether any of the ductal-derived proteins mentioned above reach the fluid in these later parts of the system is unknown.

The movements of water and ions take place across the salivary gland epithelium by the various processes outlined above; the ultimate source of water and ions in saliva is the blood plasma and the interstitial fluid derived from it.

Composition of saliva

The fluid which is normally present in the mouth, forming a thin layer between the surfaces of the cheeks and lips, the teeth, the tongue and the palate, is a mixture of secretions with a substantial component from the minor glands. Mixing of secretions takes place, but fluids near the orifices of the ducts of the major glands will obviously be nearer in composition to the appropriate secretion. During mastication when there is increased flow and the effective volume of the mouth which is available for saliva is increased by the presence of food: the saliva in the mouth is mixed with the food. It is difficult therefore to define the resting environment of the teeth, with their covering of dental plaque, and that of the oral soft tissues, in terms of the different salivary secretions. The mixed secretions which are collected by expectoration (spitting) are termed whole saliva or mixed saliva by different writers; neither of these terms is entirely satisfactory and the term 'oral fluid' sometimes used in USA is a better alternative. Such terminology also avoids the implication that the expectorated fluid contains only the secretions of salivary glands. In fact the fluid contains a contribution from gingival crevicular fluid, bacteria and white blood cells. It is rare for it to contain food particles except during and immediately after food intake.

There is a much greater amount of information available in relation to parotid saliva than to the other secretions, largely because there is an effective method in the Lashley (Carl son-Crittenden) cannula or cup for the easy collection of large volumes of a pure secretion. A superficial judgment suggests that whole saliva (oral fluid) should give the best assessment of the nature of the oral environment, but if the calculations on the volume of saliva normally in the mouth are valid the possibility exists of major differences in different parts of the mouth. It would seem appropriate therefore to describe the composition of saliva principally in terms of whole saliva (oral fluid).

Ionic composition

Calcium and phosphate

In terms of ionic composition the three ions in saliva which concern the dentist most are calcium, phosphate and hydrogen carbonate - the first two because they will help to prevent dissolution of dental enamel and the last because of its buffering power. There are two other ions which play a part in the protection of the enamel surface: fluoride because of its ability to substitute into the hydroxyapatite lattice, and thiocyanate because of its antibacterial activity when converted to hypothiocyanate by salivary lactoperoxidase. Calcium and phosphate are present in whole saliva typically at 1.4 mmol/l and 6 mmol/l, respectively, in unstimulated saliva and 1.7 and 4 mmol/l in stimulated saliva. The values for calcium are misleading because they are for total calcium and only around 50% of calcium in saliva is present in an ionic form – about 40% is complexed with other ions and about 10% bound by salivary protein. Phosphate, on the other hand, is almost all in the ionic form perhaps 10% being organic phosphate and in some subjects a small amount of pyrophosphate is present. If these values are substituted into the equation for the solubility product of hydroxyapatite, it is apparent that hydroxyapatite is unlikely to dissolve in saliva at a pH around 6.0 – the pH of resting saliva. However, increase in pH or in calcium or phosphate concentration could result in precipitation of calcium salts as in the formation of dental calculus. It is difficult to predict how calcium concentrations in whole saliva will vary at different flow rates because, although in individual secretions calcium concentrations increase with flow rate, whole saliva will have a smaller proportion of submandibular saliva and a greater proportion of parotid saliva at high flow rates and parotid saliva has only about half the calcium concentration of submandibular saliva. Phosphate concentrations in saliva tend to decrease at higher rates of flow. This may be because phosphate is probably secreted into saliva in the ducts and more rapidly secreted saliva traverses the ducts more quickly. If

this explanation is correct the output of phosphate in unit time should be roughly constant. Phosphate concentrations are particularly low in minor gland saliva. The higher calcium concentration in submandibular saliva helps to explain why calculus is particularly likely to form on the lingual side of the lower incisors. Calculus formation on the buccal surface of the upper first molar - another common site - is more difficult to explain. Whilst calcium and phosphate concentrations in saliva have not been shown to relate to overall calculus formation, individuals with more pyrophosphate in their saliva form less calculus. This is not surprising as pyrophosphate is a well-known inhibitor of calcification and is now used as the active ingredient of anti-tartar toothpastes.

Hydrogen carbonate

Hydrogen carbonate concentrations are low in unstimulated saliva from all the glands but increase markedly at fast flow rates. Hydrogen carbonate is the major buffer in saliva: it pushes the pH of stimulated saliva up towards pH 8.0 and is active as a buffer around the so-called critical pH of 5.6 in dental plaque - the pH at which enamel begins to dissolve in saliva. It can easily be shown that the pH fall in dental plaque exposed to sugar solutions can be greatly reduced by saliva collected at fast flow rates and that the pH fall in dental plaque on a tooth surface from which saliva is excluded is greater than that in the presence of saliva. Thus hydrogen carbonate is an effective defence against the acid produced by cariogenic bacteria. The lower caries experience of subjects with faster saliva flow rates may be due to this factor. A paper strip test is available (formerly known as Dentobuff©, but now Vivacult BCO) which measures salivary buffer capacity as a means of assessing susceptibility to dental caries. The hydrogen carbonate is ultimately derived from the carbon dioxide generated by metabolic activity in the salivary glands, which contain much carbonic anhydrase and can readily hydrate the carbon dioxide. This explains the

increased concentration at higher flow rates. The ion is in equilibrium with dissolved carbon dioxide in saliva, but loss of carbon dioxide from saliva increases its alkalinity and so calcium salts may precipitate out from saliva on standing.

Glucose monitoring: The goal of diabetes treatment is to keep your blood sugar level as close to normal as possible. Home blood glucose monitoring helps people with diabetes to monitor their blood glucose levels throughout the day. For millions of Americans with diabetes, regular home testing of blood glucose levels is critical in controlling their disease. Self-monitoring of blood glucose (SMBG) is an important part of the care and management of people with diabetes. The first step is to eat a healthy diet and exercise regularly. Monitoring allows them to make immediate changes in their treatment plan when needed.

There are a variety of meters available for use in home blood glucose testing. It is important to use SMBG effectively and efficiently since it is a relatively expensive

In Persons with diabetes may have to check their blood sugar levels up to four times a day. Blood sugar levels can be affected by several factors, including the following:

- diet
- diabetes medication
- exercise
- stress
- illness

intervention and patients often find it is painful.

Extra monitoring of blood glucose should be done when:

- Low blood sugar is suspected
- More physical activity is done

- Weight loss or gain occurred
- Pregnant, or planning a pregnancy
- One is not sure about symptoms of low blood sugar
- Levels too high or too low
- Intensive insulin therapy

Interest in monitoring the glucose concentrations of diabetic patients has increased since the publication of the diabetes control and complications trials report showing that tight control of blood glucose concentrations, by frequent testing and concomitant adjustment of insulin doses, decreases long term complications resulting from diabetes.

A computer simulation based on the Diabetes control and complication trials results estimates an additional 5 years of life, 8 years of sight, 6 years of free - from kidney disease, and 6 years free – from- amputations for a diabetic following the tight control using the standard regimen.[119]

About 1-2 billion blood glucose tests are done per year by diabetic people at work, at home, at restaurants and at a wide variety of other places.[120]

The data obtained is used for testing and to determine the amount of insulin that the patients need for safety of exercise and weather extra food or a glucose tablet is needed for a blood glucose concentration that is too low.[121]

Using real time data for evaluating options and making decision about the treatment of a variety of conditions is appealing to both patients and health professionals.[6] Health professionals also use this information to determine blood glucose control and patterns of abnormal blood glucose that may require alterations in medical therapy.[122]

Despite the tremendous value of self monitoring of blood glucose for the treatment of diabetes, many patients find the testing onerous and some refuse to perform the measurement. These complaints are largely justified because self monitoring of blood glucose is painful, inconvenient, messy, embarrassing and above all expensive.

Most patients consider the finger lancing necessary for obtaining blood for self monitoring of glucose to be the most painful part of diabetes therapy. The direct pain of the lancet is several folds greater than that of an insulin syringe because of the greater lancet thickness, the site of lancing (the finger tip usually used for blood glucose monitoring has many more pain fibers than does the thigh often used for insulin injections) and other factors. In addition, patients frequently complain of residual pain at the site of lancing that may last several hours and be especially distressing during important tasks, such as opening a bottle or typing.

Current techniques of blood glucose monitoring are inconvenient because they are limited by location, equipment and supplies. Patients usually start the procedure by washing their hands which requires a sink or other water supply. They must carry a lancer, lancets, blood glucose strips and a meter. Frequently they also need tissue, a water supply or a clock. The procedure takes several minutes and they must bring a logbook for their records. Many patients carry a separate bag to accommodate all these supplies. The procedure is messy. A drop of blood must be obtained from a finger and transferred onto a blood glucose strip. Unfortunately, the blood is often not limited to the strip.

Non invasive monitoring of glucose has been of particular interest because of the pain associated with invasive self monitoring. Ease of use and reduction of pain can encourage more frequent testing and hence tighter control of the glucose concentration. Patient care need and the commercial importance of NI glucose monitoring has led to a

flurry of "research" by entrepreneurial and commercial concerns that have been published mainly in patent literature. However a large number of NI glucose patents lack scientific rigor and some may be based on wrong or unproved assumptions.[8]

Interest has been increasing recently in non-invasive diagnostic testing. Some of this storm from the AIDS epidemic in the west, which has provided a new rationale for hemophilia, while other factors include new development in home based diagnostic tests and a demand of samples to be collected in the home or work place. Diagnostic tests based on fluid generally use blood and urine and less frequently the esoteric fluids such as saliva, sweat and tears.[9]

Researchers are developing other methods of non invasive monitoring. Potential ways to determine blood glucose levels include

- Shining a beam of light onto the skin or through body tissue
- Measuring the energy waves (infrared, radiation) emitted by the body
- Applying radio waves to the fingertip
- Using ultrasound
- Checking the thickness (also called the viscosity) of fluids in tissue underneath the skin[10]

An NI body glucose monitoring device is defined by Omar S. Khalil in a review as a device that comes in contact with or remotely senses, a human body part, without protrusion through membranes or sampling a body fluid for analysis external to the part.[8]

Diagnostic tests based on fluid generally use blood and urine and less frequently the esoteric fluids such as saliva, sweat and tears[9] salivary glucose concentrations in patients with diabetes mellitus – a minimally invasive technique for monitoring blood glucose levels

A urine glucose test determines whether or not glucose (sugar) is present in the urine. Glucose will overflow into the urine only when the blood glucose level is high, that is, too

high for the kidneys to stop it spilling over into the urine. In most people, blood glucose levels above 10 mmol of glucose per liter of plasma will cause glucose to appear in the urine. This level is called the 'renal threshold' for glucose. However, the renal threshold for glucose can be lower in some people who are otherwise healthy, during pregnancy, and in people who have a kidney disorder. In these people, glucose may be present in the urine despite the blood glucose being normal. This can sometimes make urine glucose tests difficult to interpret.

Limitations of urine glucose monitoring

- A urine glucose test does not reflect blood glucose level at the time of testing; instead, it gives an indication of blood glucose level over the past several hours. For example, some of the urine present in bladder may be 2 hours old, and may show glucose even though blood glucose may have normalised since then.
- A urine glucose test does not give any information about low blood glucose levels, as glucose is only found in the urine when the blood glucose level is above 10 mmol/L. That is, a negative urine glucose test may be the result of a normal blood glucose level or a dangerously low blood glucose level, with the urine glucose test unable to differentiate between the 2 situations.
- The results of a urine glucose test are influenced by the volume and concentration of urine that is passed, which will vary with the amount of fluid consumed and the fluid loss due to such things as heavy sweating or vomiting.
- Urine glucose tests designed for home use rely on interpreting a colour change to define the result. Subtle colour differences may be difficult to interpret.

- If a urine glucose test is not read at the specified time after applying the urine to the test strip, then the result is prone to error.
- Some medications may interfere with the results of urine glucose testing.

Advantages of urine glucose monitoring

- Urine glucose testing is easy to do: just dip the test strip in the urine and read the result at the allocated time.
- It is less painful than blood glucose monitoring — no finger pricks to collect blood!

Urine test strips are less costly than buying a blood glucose monitor and its test strips.[123]

Sweat is relatively easily obtained but the glucose concentration lags significantly behind blood glucose. Methods to increase sweating have been developed and seem to increase the timeliness of the sweat glucose measurement.[12]

The assay of saliva is an increasing area of research with implications for basic clinical purpose. Although this biological fluid is easy to manipulate and collect, careful attention must be directed to limit variation in specimen integrity. Recently the use of saliva has provided a substantial addition to the diagnostic armamentarium as an investigative tool for disease process and disorders. In addition to its oral indications, the analysis of saliva provides important information about the functioning of various organs in the body.[124]

Saliva offers distinctive advantages over serum because it can be collected non invasively by individuals with modest training. Furthermore saliva may provide a cost effective approach for the screening of large populations. Saliva may provide a cost effective approach for the screening of large populations.

Some systemic diseases affect salivary glands directly or indirectly and may influence the quantity of saliva that is produced as well as the composition of the fluid.

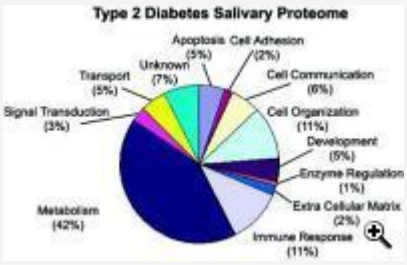
These characteristic changes may contribute to the diagnosis and early detection of these diseases.

Hereditary diseases such as cystic fibrosis celiac disease, 21-hydroxylase deficiency can be detected in early age. Salivary analysis may aid in early detection of certain malignant tumors by use of tumor markers, infectious diseases like helicobacter pylori, pigeon breeders disease, Lyme disease, viral disease like measles, mumps, rubella. Saliva has been used in new born infants for detection of retrovirus infection. Saliva was also found to be a reliable alternative to serum for identification of virus HSV-1 and parvovirus B19 and HIV. Saliva has been proposed for the monitoring of systemic levels of drugs. The analysis of endocrine function is also possible with the use of saliva, salivary cortisol levels, salivary aldosterone levels, estradiol levels.[118]

Despite few limitations, the use of saliva for diagnostic purposes is increasing in popularity due to its many potential advantages. It provides an attractive alternative to more invasive, time consuming, complicated glucose monitoring tests as saliva can be collected in a non invasive manner by individuals with modest training including patients.[118]

The test, developed by the research team led by Paturi V. Rao, is based on chemical recognition of biomarkers in the patients' saliva. The scientists analyzed saliva samples from type 2 diabetes patients and healthy individuals. They sought protein biomarkers of the disease. Eventually, they identified 65 proteins that appeared twice as often in the patients' samples than in the healthy samples.

The biomarkers found are proteins responsible of various functions. A majority of them belong to pathways regulating metabolism and immune response. The research team also demonstrated a trend of relative increases in marker abundance with progression from the pre-diabetic to the diabetic state. This proteomic analysis of the human saliva in type 2 diabetes provides the first global view of potential mechanisms altered in diabetic saliva and their utility in detection and monitoring of diabetes. Further characterization of these markers in additional groups of subjects may provide the basis for new, non-invasive tests for diabetes screening, detection, and monitoring.



Functional annotation of human whole saliva in type-2 diabetes. The majority of the proteins are predicted to have metabolic and immune response functions (Credit: American Chemical Society)

TFOT has recently covered a three drug treatment that could help type 1 diabetes patients, found by researchers at the Beth Israel Deaconess Medical Center (BIDMC) in Boston. TFOT has also covered a saliva test that could identify a heart attack in progression, developed by researchers from the University of Texas at Austin.[125]

Saliva has been used reliably for reflecting and monitoring the blood glucose concentration in the patients of diabetes mellitus. [126,127,128,9]

Hence the present study was undertaken to quantitatively estimate the amount of salivary glucose levels in type-2 diabetic patients and explore the possibility of using saliva to reflect the glucose concentration in blood, thereby making self-measurement of glucose less invasive.