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D I P L O M A T H E S I S

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Pharmacological aspects of Diabetes Mellitus

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CONTENTS

Aim of thesis

The aim of this thesis is to give a brief aspect of the most common endocrine disorder of the western world which is diabetes mellitus. It will also try to cover the main complications of the disease and the ways we have currently available or we will have in the near future to combat it.

We do not aspire to give a detailed analysis of it but rather to mention a simplified description of the pathogenesis of diabetes and how it affects each system of the human body separately but also the organism as a whole.

We will also try to cover most of the treatment methods available today and also provide a brief comparative study highlighting their main advantages and disadvantages. There is going to be a note of the most current breakthroughs in treating the disease and the possible impact they are going to have in the future medical practice.

This thesis does not aspire to be a specialist's reference essay but rather a comprehensive introduction to a very complex and largely unclarified medical problem which torments the human species for countless centuries and will probably continue to do so in the future. It also tries to present to the reader the ways that the science of pharmacy has provided or will provide in the near future to treat it and how these ways work in the human body to accomplish that.

We are going to talk about their beneficial effects but also about their side effects and disadvantages and we are going to talk about the new hope that modern pharmaceutical research promises for the times to come.

Diabetes is a silent killer that knows no race, age, social or economic group preference. It affects the most crucial systems of our bodies and its chronic course inevitably leads to increased morbidity and mortality. Diabetes takes its toll not only on the large number of people who suffer from it but on all of us as it strikes almost in every family and causes health care systems all around the world to spend billions in a struggle which seems futile to many of us.

This is the final aim of this report .To prove that although our knowledge is not complete we are able to strike back at the problem. To prove that all the effort put in it has significant results in increasing the life expectancy and the quality of life of diabetic patients. And to remind that pharmacists around the world continue to ask the questions and sooner or later they will have their answers.

Introduction

Diabetes is any disorder characterized by excessive urine excretion. The most common form of diabetes is **diabetes mellitus,** a metabolic disorder in which there is an inability to oxidize carbohydrate due to disturbances in insulin function. Other forms of diabetes include diabetes insipidus and brittle diabetes. Diabetes insipidus is the result of a deficiency of antidiuretic hormone. The major symptom of diabetes insipidus (excessive urine output) results from an inability of the kidneys to resorb water. Brittle diabetes is a form that is very difficult to control. It is characterized by unexplained oscillations between hypoglycemia and acidosis.

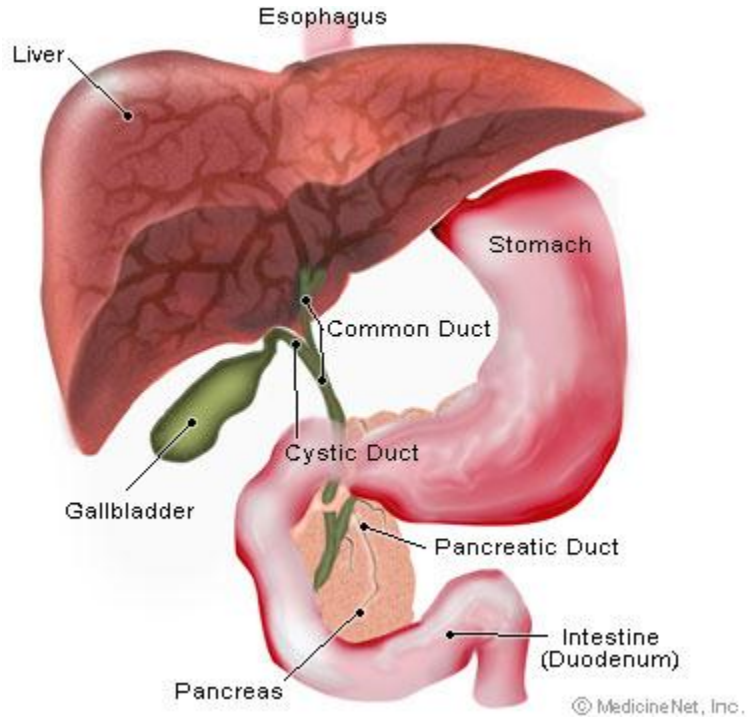
Diabetes mellitus is a group of metabolic diseases characterized by high blood sugar (glucose) levels, which result from defects in insulin secretion, or action, or both. Diabetes mellitus, commonly referred to as diabetes, was first identified as a disease associated with “sweet urine," and excessive muscle loss in the ancient world. Elevated levels of blood glucose (hyperglycaemia) lead to spillage of glucose into the urine, hence the term sweet urine. Normally, blood glucose levels are tightly controlled by insulin, a hormone produced by the pancreas. that is needed to convert sugar, starches and other food into energy needed for daily life. Insulin lowers the blood glucose level. When the blood glucose elevates (for example, after eating food), insulin is released from the pancreas to normalize the glucose level. In patients with diabetes, the absence or insufficient production of insulin causes hyperglycaemia. Diabetes is a chronic medical condition, meaning that although it can be controlled, it lasts a lifetime.

Historical development

In the fall of 1920 Dr. Frederick Banting had an idea that would unlock the mystery of the dreaded diabetes disorder. Before this, for thousands of years, a diabetes diagnosis meant wasting away to a certain death. Working at a University of Toronto laboratory in the very hot summer of 1921 Fred Banting and Charles Best were able to make a pancreatic extract which had anti diabetic characteristics. They were successful in testing their extract on diabetic dogs. Within months Professor J. J. R. MacLeod, who provided the lab space and general scientific direction to Banting and Best, put his entire research team to work on the production and purification of insulin. J.B. Collip joined the team and with his technical expertise the four discoverers were able to purify insulin for use on diabetic patients. The first tests were conducted on Leonard Thompson early in 1922. These were a spectacular success. Word of this spread quickly around the

world giving immediate hope to many diabetic persons who were near death. A frenzied quest for insulin followed. Some patients in a diabetic coma made miraculous recoveries.

While insulin is not a cure, this medical discovery has and continues to save millions of lives world-wide. The production of insulin has changed a great deal since 1922. Modern science and technology has made high quality insulin and delivery systems available to diabetic persons.



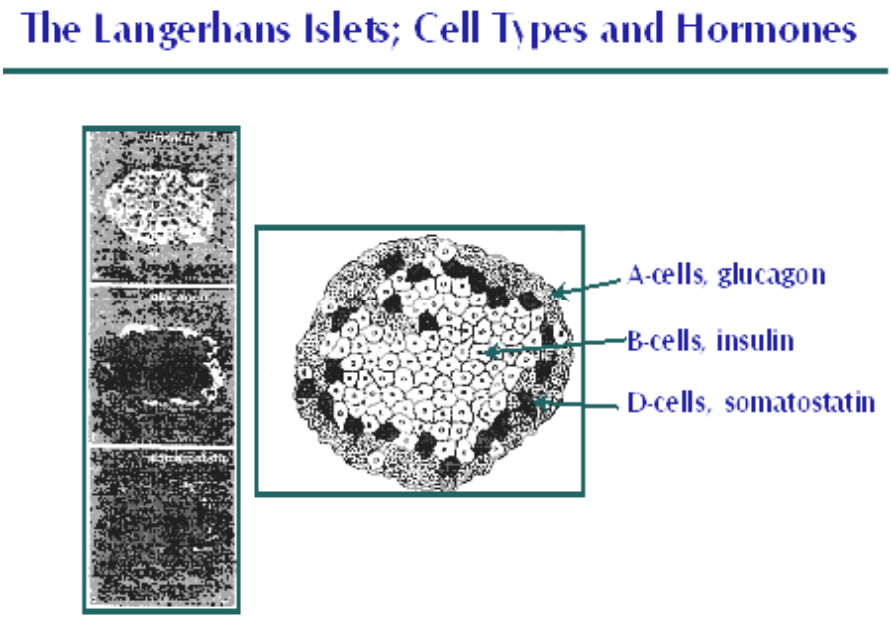
Diabetic disease

There are two widely known forms of diabetes. **TYPE 1** is a failure of the pancreas to produce insulin. Daily injection of insulin replacement is the treatment, itself a triumph of twentieth century science. **TYPE 2** is insulin resistance or impaired glucose tolerance. This model of two forms of diabetes may be too simple. Diabetes may be a whole family of related diseases.

The Islets of Langerhans

The pancreatic Islets of Langerhans are the sites of production of insulin,

glucagon and somatostatin. The small pictures below show immunofluorencence images in which antibodies specific for these hormones have been coupled to a fluorescence marker. Most of the central area of the Islets are composed of the insulin-producing B-cells. These account for about 80% of the Islets. The periphery of these organelles contains the A-cells that produce glucagon. A small number of D-cells that produce somatostatin are also seen. All of these differing cells are in close proximity with one another. While they primarily produce hormones to be circulated in blood (endocrine effects), they also have marked paracrine effects. That is, the secretion products of each cell type exert actions on adjacent cells within the Islet.

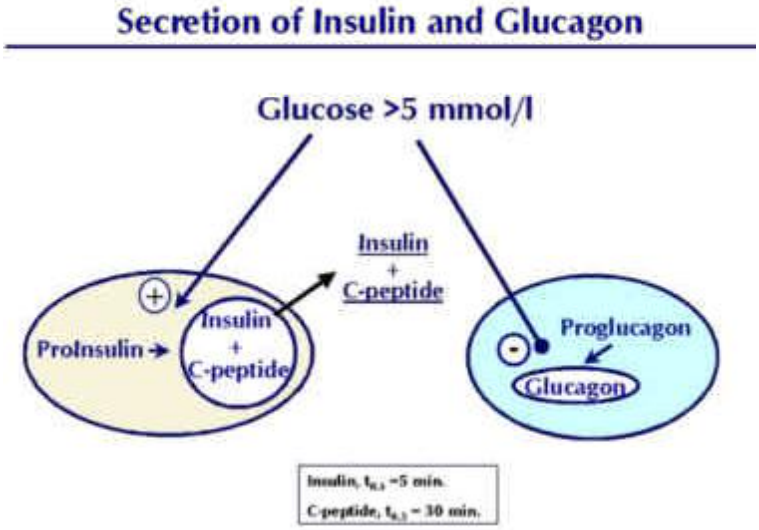


Secretion of insulin and glucagon

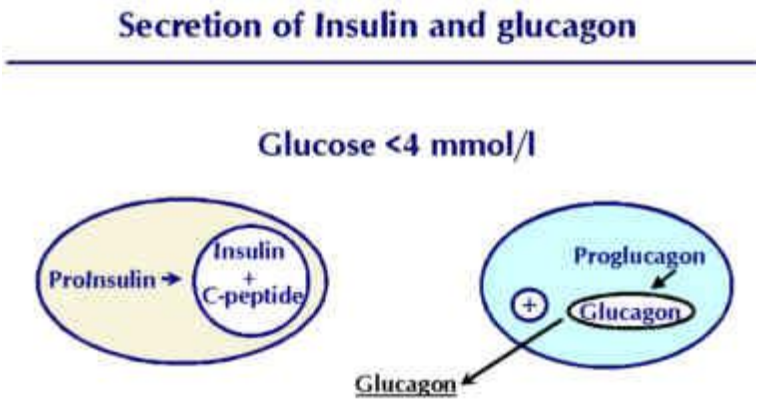
The nutrient-regulated control of the release of these hormones manages metabolism and blood levels of glucose, fatty acids, triglycerides and amino acids.

These are responsible for homeostasis; the minute-to-minute regulation of metabolism leading to a stable inner milieu. The mechanisms involved are extremely complex and are still not completely understood. Modern medical treatment of diabetes (rapidly becoming "public enemy number one") is based on insight into these mechanisms.

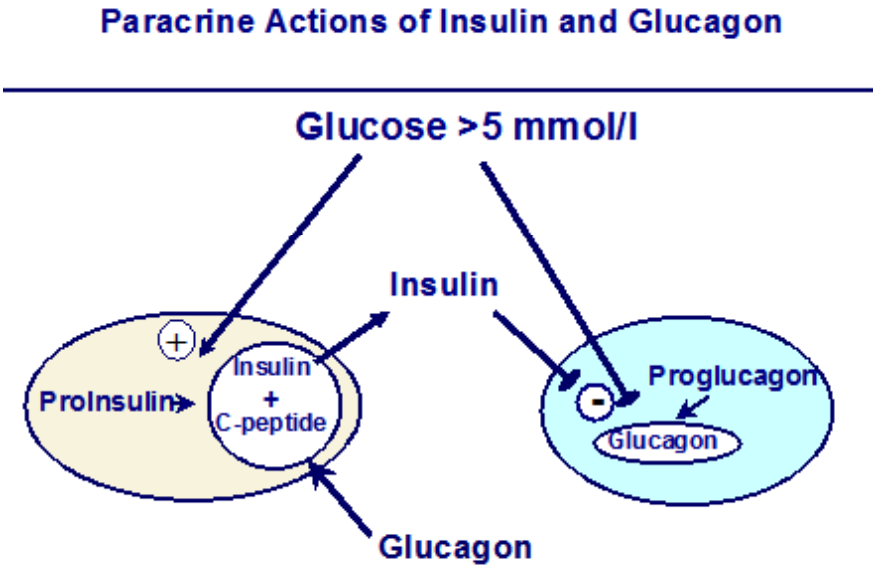
Both insulin and glucagon are initially synthesized as larger "prepro-hormones" and "pro-hormones". These are then cleaved to give active hormones and the remains of the longer peptide chains. In the case of insulin, this excess peptide is known as C-peptide or connecting peptide. It is of interest because it has a much longer half-life than insulin and is released simultaneously with the hormone. Insulin has a half-life of about 5 minutes. Secretion of insulin is, therefore, difficult to measure. One can follow insulin secretion by measuring the level of C-peptide which has a half-life of about 30 minutes. When blood glucose levels increase over about 5 mmol/l the beta-cells increase their output of insulin and C-peptide. The glucagon-producing alpha-cells remain quiet, and hold on to their hormone.



A fall in blood glucose under about 4 mmol/l leads to a pronounced decrease in insulin secretion. The alpha-cells become active and deliver glucagon to the blood. There is a total secession of secretion of insulin or glucagon at high or low glucose levels. Both cell types release their hormones simultaneously at a basal level. This is augmented in response to alterations in blood glucose levels or consumption of food. It is the balance between insulin and glucagon (the resulting molar ratios of these hormones) that controls metabolism.



As already mentioned, the cells of the Langerhans Islets are tightly packed. This results in high concentrations of each hormone within the organelle. Increases in insulin levels inhibit glucagon release from α-cells. This paracrine effect is a basic element in insulin's control of both hepatic gluconeogenesis and lipolysis in adipose tissue.

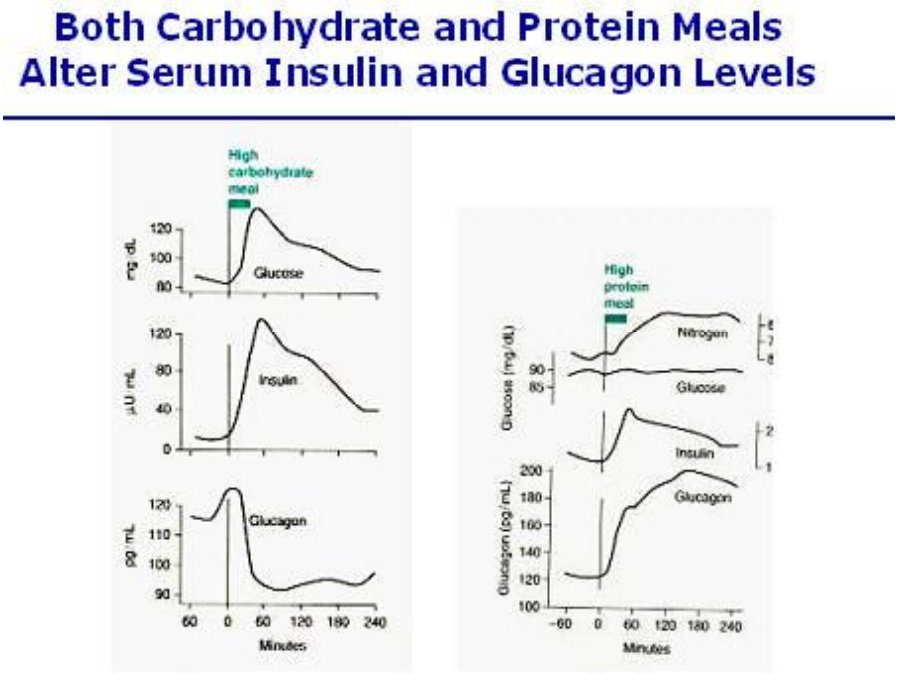


Glucagon secretion increases when blood sugar levels are diminished. These are, of course, periods when insulin action is not called. One might think that glucagon had a negative paracrine action on ß-cells, but that is not the case. Glucagon does affect these insulin-secreting cells, but that effect is positive! That is, glucagon released between meals primes ß-cells so that they release increased amounts of insulin when glucose levels rise. Glucagon's action is coupled to production of a "second messenger", cyclic AMP. Increased levels of cAMP are an

important controlling factor in insulin secretion. This seems to be the basic mechanism for a new class of drugs now coming in use for regulation of insulin secretion in diabetes type 2.

Insulin and Glucagon secretion is coordinated (Stryer pg.773-774)

Insulin has many actions, the most well-known is stimulation of glucose and amino acid uptake from the blood to various tissues. This is coupled with stimulation of anabolic processes (or synthetic reactions) such as glycogen, protein and lipid synthesis. Glucagon has opposing effects, causing release of glucose from glycogen and stimulation of gluconeogenesis and lipolysis. The balance between these two hormones holds metabolism "on the line", promoting a stable inner metabolic milieu (or homeostasis).



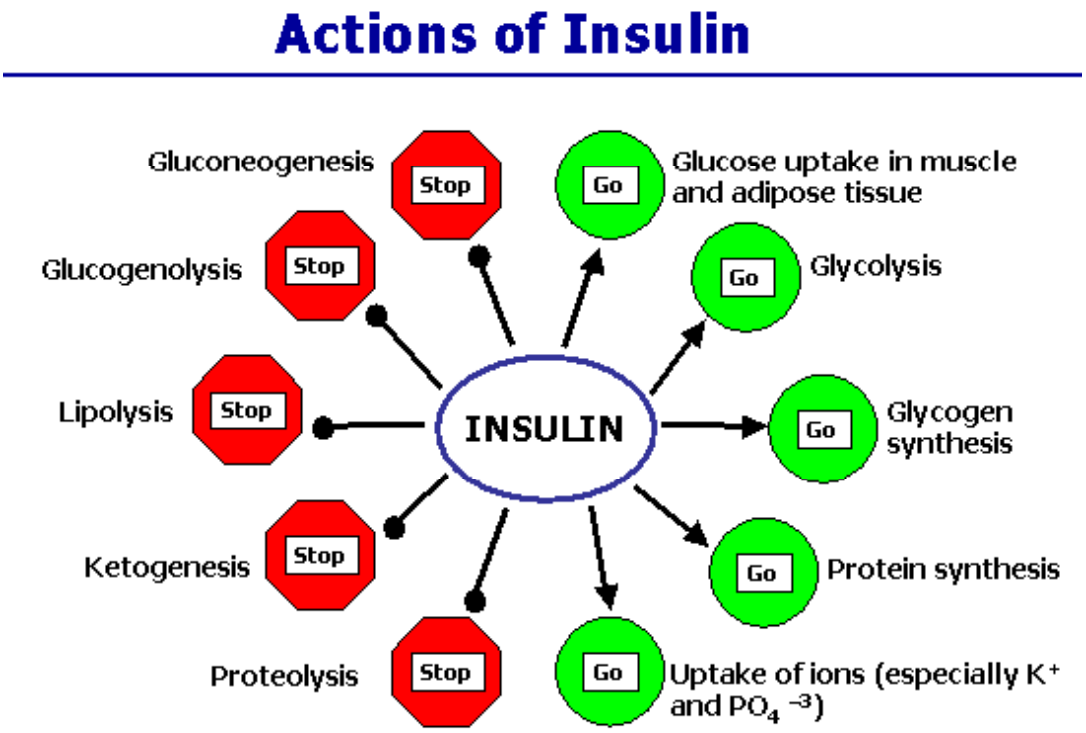
Modified from Marks, Basic Medical Biochemistry, 2. ed, 2004

Consumption of carbohydrates triggers release of insulin from beta cells. Alpha cells become inhibited and cease to secrete glucagon. Taken together, these actions produce a rapid return to fasting blood sugar levels and storage of glucose as glycogen or lipid.
A protein-rich meal leads to release of both insulin and glucagon. The latter stimulates gluconeogenesis and release of the newly formed glucose from the liver

to the blood stream. The very moderate rise in insulin associated with the protein meal stimulates uptake of the sugar formed in the liver by muscle and fat tissue.

Metabolic effects

Insulin signals a state of energy abundance, and activates glucose uptake, metabolism and storage as glycogen in muscle and fat tissue. These organs make up most of the body's mass. At the same time, insulin restrains processes that release stored energy; lipolysis and ketogenesis, glycogenolysis, proteolysis and gluconeogenesis.



Modified from Clinical Biochemistry, A. Gaw et al, Churchill Livingstone, Edinburgh, 1995.

Insulin signals a state of energy abundance, and activates glucose uptake, metabolism and storage as glycogen in muscle and fat tissue. These organs make up most of the body's mass. At the same time, insulin restrains processes that release stored energy; lipolysis and ketogenesis, glycogenolysis, proteolysis and gluconeogenesis. Insulin is necessary for uptake of amino acids to tissues and for protein synthesis. Insulin is the central actor in homeostasis; the stabilization of the internal milieu.

It has previously pointed out that insulin and glucagon act together to balance metabolism In general we can say that insulin favors anabolic reactions; glucagon, catabolic reactions. Put more simply, insulin favors storing energy and production of proteins while glucagon activates release of stored energy in the form of glucose or fatty acids. The actions of these two hormones on individual metabolic processes are summarized next:

Fatty acid uptake and release in fat.
Insulin: Stimulates synthesis of triglycerides (TG) from free fatty acids (FFA); inhibits release of FFA from TG.
Glucagon: Stimulates release of FFA from TG.

Liver glycogen
Insulin: Increases synthesis and thereby glucose uptake and storage.
Glucagon: Stimulates glycogenolysis and glucose release.

Liver gluconeogenesis
Insulin: Inhibits, saves amino acids.
Glucagon: Stimulates, glucose synthesized and released.

Glucose uptake, skeletal muscle
Insulin: Stimulates uptake, storage as glycogen and use in energy metabolism.
Glucagon: No receptors, no effect.

Glycogen, skeletal muscle
Insulin: Stimulates synthesis.
Glucagon: No receptors, no effect.

Amino acid uptake
Insulin: Stimulates and is necessary for protein synthesis.
Glucagon: Stimulates and is necessary for protein synthesis.

Brain (hypothalamus)
Insulin: Reduces hunger.
Glucagon: No effect.

Tissue distribution of glucose after a meal (Stryer pg. 775)

Eating a good meal does alter blood glucose levels. A normally balanced meal provides about 90 grams of glucose, mostly as polysaccharides. These are usually absorbed over a period of about 120 minutes. The glucose released from food is used as an immediate energy substrate and any excess will be stored as glycogen (and fat in the case of over-nutrition).

A prerequisite for oxidation or storage of glucose is that it is transported into cells over their plasma membrane. Uptake of larger molecules requires the

presence of specific carriers. In the case of glucose we find a family of at least five glucose transport proteins with varying characteristics. The important point is that the body's largest tissue, skeletal muscle, is dependent upon GLUT4 for uptake of glucose and that this transport must be activated by insulin or muscle activity. In adipose tissue insulin is required for storage of lipids from the diet and for control of lipolysis.

It is important that blood glucose levels after a meal are held below renal threshold for recovery of glucose from the glomerular filtrate (8-10 mmol/l). If this is exceeded, glucose is lost to the urine as is seen in diabetes. So, after a meal insulin secretion is activated, glucagon secretion is minimized, and the liver takes up glucose which is then stored as glycogen to be used to buffer blood glucose at a later time. Insulin also stimulates glucose uptake and glycogen synthesis in muscles. Muscle glycogen cannot be released to the circulation; it is used exclusively as a substrate for muscle activity. Brain's glucose uptake is constant. Around 15-18% of the ingested glucose goes to nourish the brain during the absorptive period. There is no storage form of glucose in the CNS; all of the glucose that is taken up is "burned". The brain is, therefore, extremely sensitive to reduced blood glucose levels. The liver stores excess glucose as glycogen, readying a buffer for blood glucose to meet the coming post-absorptive period. Little glucose is normally converted to fat. Overeating carbohydrates (sucrose and fructose) can and does lead to fat production and storage. The kidneys take up about 9-10% of the consumed glucose as lactate which is excreted from red blood cells. These lack mitochondria and, therefore, must release the partially oxidized glucose they use as pyruvate and lactate. Skeletal muscles dominate in the fight for blood sugar after a meal, accounting for about 50% of the total glucose uptake. Approximately half of this is stored as glycogen, the rest is used as an immediate energy substrate. Recalling that insulin is needed to activate glucose uptake in muscle (GLUT4 is the carrier here) shows that skeletal muscle must be the major target organ for insulin.
A reduction in the effect of insulin in skeletal muscle **(insulin resistance)** is the key mechanism leading to impaired glucose tolerance (IGT) and diabetes type 2.

Energy metabolism during a fast and in starvation

Between meals and during a fast:

Energy production during the absorptive period uses glucose from the diet as

substrate. The insulin to glucagon ratio is lowered during the post-absorptive period and during a fast. Insulin inhibits lipolysis in adipose tissue while glucagon is a major activator of hormone-sensitive lipase. The change in the insulin/glucagon ratio seen in fasting and between meals activates adipocyte lipolysis. Adipose tissue supplies fatty acids to drive aerobic metabolism in muscle, liver and other tissues (but not the brain, fatty acids are not taken up here). Excess fat can be converted to ketone bodies in the liver. The levels of these remain rather low and they are used as energy substrates in muscle. Glycerol arising from lipolysis cannot be reused in fat cells but is circulated to the liver where it enters gluconeogenesis.

Starvation:

The marked fall in insulin levels seen in starvation lead to an increase in plasma levels of both free fatty acid and especially ketone body levels. Most of the fatty acids liberated from adipose tissue are converted to ketone bodies (acetoacetate and beta-hydroxy butyrate) by the liver during starvation. The level of these "ketone bodies" rises abruptly during the two first weeks of starvation, and then slowly increases. When plasma ketone body levels reach about 5mmol/l they can supply the brain with around 50% of the substrate required for ATP production. Even during starvation about 50% of the brain's energy must come from glucose. From around the second week of starvation, blood glucose levels stabilize at approximately 3.5 mmol/l. At this glucose concentration, the brain can extract enough ketone bodies and glucose from blood to maintain normal activity. The conversion of fatty acids to ketone bodies allows the brain to obtain energy from the large energy reserve represented by body fat (the brain cannot take up fatty acids from the blood). Blood glucose is the factor that limits survival time in starvation. By switching brain metabolism to a 50-50 dependence upon glucose and ketone bodies survival time is greatly prolonged. The body's muscles are broken down to provide amino acids that are converted to glucose by the liver and kidneys. When the supply of amino acids becomes rate-limiting for gluconeogenesis, blood glucose levels fall and neural tissue starves and dies. (Stryer pg.775)

Classification of Diabetes mellitus

Diabetes mellitus is a heterogeneous clinical disorder with numerous causes. Two main classifications of diabetes mellitus exist, **idiopathic** and **secondary**.

Idiopathic diabetes is divided into **two main types**; insulin dependent and non-insulin-dependent.

Insulin-dependent diabetes mellitus, IDDM (more commonly referred to as **type 1** diabetes) is defined by the development of ketoacidosis in the absence of insulin therapy**.** Type 1 diabetes most often manifests in childhood (hence also called juvenile onset diabetes) and is the result of an autoimmune destruction of the beta-cells of the pancreas.

Non-insulin-dependent diabetes mellitus, NIDDM (more commonly referred to as **type 2** diabetes) is characterized by persistent hyperglycemia but rarely leads to ketoacidosis. Type 2 diabetes generally manifests after age 40 and therefore has the obsolete name of adult onset-type diabetes. Type 2 diabetes can result from genetics defects that cause both insulin resistance and insulin deficiency. There are **two main forms of type 2** diabetes:

1. Late onset associated with obesity.
2. Late onset not associated with obesity.

There is a strong correlation between obesity and the onset of type 2 diabetes with its associated insulin resistance. It should be pointed out that in the United States the proportion of the population under 40 that can be clinically defined as obese now exceeds 25%. Many children are obese and are developing type 2 diabetes at an alarming epidemic rate. The dramatic rise in obesity in the US has lead to an equally alarming increase in the percentage of the population who suffer from the **metabolic syndrome**. The metabolic syndrome is a clustering of atherosclerotic cardiovascular disease risk factors, one of which involves insulin resistance characteristic in type 2 diabetes. It should be pointed out that obesity alone does not always lead to insulin resistance as some individuals who are obese do not experience insulin resistance and conversely, some individuals who manifest insulin resistance are not obese. These latter observations point to the added role of genetics in the acquisition of insulin resistance.

Secondary, or other specific types of diabetes mellitus are the result of many causes including:

1) Maturity onset type diabetes of the young (MODY) was previously considered to be a third form of type 2 diabetes. However, with the discovery of specific mutations leading to MODY, it is now classified under secondary or other specific types of diabetes. MODY is characterized by onset prior to age 25. All cases to date have shown impaired b-cell function. Patients may also exhibit insulin resistance and late b-cell failure. Evidence indicates that mutations in 10-12 different genes have been correlated with the development of MODY. Mutations in

the 6 genes described here are all clearly correlated to MODY:
MODY1: the transcription factor identified as hepatic nuclear factor-4a (HNF-4a).
MODY2: pancreatic glucokinase
MODY3: the transcription factor HNF-1a. This gene is also called hepatocyte transcription factor-1 (TCF1).
MODY4: the homeodomain transcription factor insulin promoter factor-1 (IPF-1). This gene is more commonly called PDX1 derived from pancreas duodenum homeobox-1.
MODY5: the transcription factor HNF-1b. This gene is also called hepatocyte transcription factor-2 (TCF2).
MODY6: the bHLH transcription factor NeuroD1. NeuroD1 was first identified as a neural fate-inducing gene. The hamster beta-2 gene, shown to regulate insulin transcription is identical to NeuroD1 so the gene is often called NeuroD/b2.
2. Pancreatic disease: Pancreatectomy leads to the clearest example of secondary diabetes. Cystic fibrosis and pancreatitis can also lead to destruction of the pancreas.
3. Endocrine disease: Some tumors can produce counter-regulatory hormones that oppose the action of insulin or inhibit insulin secretion. These counter-regulatory hormones are glucagon, epinephrine, growth hormone and cortisol.

a. Glucagonomas are pancreatic cancers that secrete glucagon.
b. Pheochromocytomas secrete epinephrine.
c. Cushing syndrome results in excess cortisol secretion.
d. Acromegaly results in excess growth hormone production.

4. Drug-induced diabetes; treatment with glucocorticoids and diuretics can interfere with insulin function.

5. Anti-insulin receptor autoantibodies (Type B insulin resistance)
6. Mutations in the insulin gene
7. Mutations in insulin receptor gene which lead to the syndromes listed below. Two clinical features are common in all syndromes that result from mutations in the insulin receptor gene: acanthosis nigricans and hyperandrogenism (the latter being observed only in females).

a. Leprachaunism
b. Rawson-Mendenhall syndrome
c. Type A insulin resistance

8. Gestational diabetes; this syndrome sets in during pregnancy and usually resolves itself following childbirth.
9. Many other genetic syndromes have either diabetes or impaired glucose

tolerance associated with them; lipoatrophic diabetes, Wolfram syndrome, Down syndrome, Klinefelter syndrome (XXY males), Turner syndrome, myotonic dystrophy, muscular dystrophy, Huntington disease, Friedrich ataxia (associated with deficiency in purine nucleotide phosphorylase), Prader-Willi syndrome, Werner syndrome, Cockayne syndrome, and others.

Insulin-Dependent Diabetes Mellitus (IDDM)

Etiology of IDDM

Type 1 diabetes has been shown to be the result of an **autoimmune reaction** to antigens of the islet cells of the pancreas. There is a strong association between IDDM and other endocrine autoimmunities (e.g. Addison disease). Additionally, there is an increased prevalence of autoimmune disease in family members of IDDM patients.

Types of Autoantibodies:

1. Islet cell cytoplasmic antibodies: The primary antibodies found in 90% of type diabetics are against islet cell cytoplasmic proteins (termed ICCA, islet cell cytoplasmic antibodies). In non-diabetics ICCA frequency is only 0.5% - 4%. The presence of ICCA is a highly accurate predictor of future development of IDDM. ICCA are not specific for the b-cells and recognize antigens in other cell types in the islet. However, the autoimmune attack appears to selectively destroy b-cells. Therefore, the antibodies may play a primary role in the destruction of islet cells. It is an equally likely possibility that the production of anti-islet antibodies occurs as a result of the destruction of b-cells. Whether a direct cause or an effect of islet cell destruction, the titer of the ICCA tends to decline over time.

2. Islet cell surface antibodies: Autoantibodies directed against cell-surface antigens (ICSA) have also been described in as many as 80% of type 1 diabetics. Similar to ICCA, the titer of ICSA declines over time. Some patients with type 2 diabetes have been identified that are ICSA positive.

3. Specific antigenic targets of islet cells: Antibodies to glutamic acid decarboxylase (GAD) have been identified in over 80% of patients newly diagnosed with IDDM. Like ICCA, anti-GAD antibodies decline over time in type 1 diabetics. The presence of anti-GAD antibodies is a strong predictor of the future development of IDDM in high-risk populations. Anti-insulin antibodies (IAA) have been identified in IDDM patients and in relatives at risk to develop IDDM. These IAA are detectable even before the onset of insulin therapy in type 1 diabetics. IAA are detectable in around 40% of young children with IDDM.

Pathophysiology of IDDM

The autoimmune destruction of pancreatic b-cells leads to a deficiency of insulin secretion. It is this loss of insulin secretion that leads to the metabolic derangements associated with IDDM. In addition to the loss of insulin secretion, the function of pancreatic a-cells is also abnormal. There is excessive secretion of glucagon in IDDM patients. Normally, hyperglycemia leads to reduced glucagon secretion. However, in patients with IDDM, glucagon secretion is not suppressed by hyperglycemia. The resultant inappropriately elevated glucagon levels exacerbates the metabolic defects due to insulin deficiency. The most pronounced example of this metabolic disruption is that patients with IDDM rapidly develop diabetic ketoacidosis in the absence of insulin administration. If somatostatin is administered to suppress glucagon secretion, there is a concommitant suppression in the rise of glucose and ketone bodies. Particularly problematic for long term IDDM patients is an impaired ability to secrete glucagon in response to hypoglycemia. This leads to potentially fatal hypoglycemia in response to insulin treatment in these patients.

Although insulin deficiency is the primary defect in IDDM, in patients with poorly controlled IDDM there is also a defect in the ability of target tissues to respond to the administration of insulin. There are multiple biochemical mechanisms that account for this impairment of tissues to respond to insulin. Deficiency in insulin leads to elevated levels of free fatty acids in the plasma as a result of uncontrolled lipolysis in adipose tissue. Free fatty acids suppress glucose metabolism in peripheral tissues such as skeletal muscle. This impairs the action of insulin in these tissues, i.e. the promotion of glucose utilization. Additionally, insulin deficiency decreases the expression of a number of genes necessary for target tissues to respond normally to insulin such as glucokinase in liver and the GLUT 4 class of glucose transporters in adipose tissue. The major metabolic derangements which result from insulin deficiency in IDDM are impaired glucose, lipid and protein metabolism.

Glucose Metabolism: Uncontrolled IDDM leads to increased hepatic glucose output. First, liver glycogen stores are mobilized then hepatic gluconeogenesis is used to produce glucose. Insulin deficiency also impairs non-hepatic tissue utilization of glucose. In particular in adipose tissue and skeletal muscle, insulin stimulates glucose uptake. This is accomplished by insulin-mediated movement of glucose transporter proteins to the plasma membrane of these tissues. Reduced

glucose uptake by peripheral tissues in turn leads to a reduced rate of glucose metabolism. In addition, the level of hepatic glucokinase is regulated by insulin. Therefore, a reduced rate of glucose phosphorylation in hepatocytes leads to increased delivery to the blood. Other enzymes involved in anabolic metabolism of glucose are affected by insulin (primarily through covalent modifications). The combination of increased hepatic glucose production and reduced peripheral tissues metabolism leads to elevated plasma glucose levels. When the capacity of the kidneys to absorb glucose is surpassed, **glucosuria** ensues. Glucose is an osmotic diuretic and an increase in renal loss of glucose is accompanied by loss of water and electrolytes, termed **polyuria**. The result of the loss of water (and overall volume) leads to the activation of the thirst mechanism (**polydipsia**). The negative caloric balance which results from the glucosuria and tissue catabolism leads to an increase in appetite and food intake (**polyphagia**).

Lipid Metabolism: One major role of insulin is to stimulate the storage of food energy following the consumption of a meal. This energy storage is in the form of glycogen in hepatocytes and skeletal muscle. Additionally, insulin stimulates hepatocytes to synthesize triglycerides and storage of triglycerides in adipose tissue. In opposition to increased adipocyte storage of triglycerides is insulin-mediated inhibition of lipolysis. In uncontrolled IDDM there is a rapid mobilization of triglycerides leading to increased levels of plasma free fatty acids. The free fatty acids are taken up by numerous tissues (however, not the brain) and metabolized to provide energy. Free fatty acids are also taken up by the liver. Normally, the levels of malonyl-CoA are high in the presence of insulin. These high levels of malonyl-CoA inhibit carnitine palmitoyltransferase I, the enzyme required for the transport of fatty acyl-CoA's into the mitochondria where they are subject to oxidation for energy production. Thus, in the absence of insulin, malonyl-CoA levels fall and transport of fatty acyl-CoA's into the mitochondria increases. Mitochondrial oxidation of fatty acids generates acetyl-CoA which can be further oxidized in the TCA cycle. However, in hepatocytes the majority of the acetyl-CoA is not oxidized by the TCA cycle but is metabolized into the ketone bodies, acetoacetate and b-hydroxybutyrate. These ketone bodies leave the liver and are used for energy production by the brain, heart and skeletal muscle. In IDDM, the increased availability of free fatty acids and ketone bodies exacerbates the reduced utilization of glucose furthering the ensuing hyperglycemia. Production of ketone bodies, in excess of the organisms ability to utilize them leads to ketoacidosis. In diabetics, this can be easily diagnosed by smelling the breath. A spontaneous breakdown product of acetoacetate is acetone which is volatilized by

the lungs producing a distinctive odor.

Normally, plasma triglycerides are acted upon by lipoprotein lipase (LPL), an enzyme on the surface of the endothelial cells lining the vessels. In particular, LPL activity allows fatty acids to be taken from circulating triglycerides for storage in adipocytes. The activity of LPL requires insulin and in its absence a hypertriglyceridemia results.

Protein Metabolism: Insulin regulates the synthesis of many genes, either positively or negatively that then affect overall metabolism. Insulin has a global effect on protein metabolism -- increasing the rate of protein synthesis and decreasing the rate of protein degradation. Thus, insulin deficiency will lead to increased catabolism of protein. The increased rate of proteolysis leads to elevated concentrations in plasma amino acids. These amino acids serve as precursors for hepatic and renal gluconeogenesis. In liver, the increased gluconeogenesis further contributes to the hyperglycemias seen in IDDM.

Non-Insulin-Dependent Diabetes Mellitus (NIDDM)

Etiology of NIDDM

NIDDM is characterized by a lack of the need for insulin to prevent ketoacidosis. Type 2 diabetes refers to the common form of idiopathic NIDDM. NIDDM is not an autoimmune disorder, however, there is a strong genetic correlation to the susceptibility to NIDDM. The susceptibility genes that predispose one to NIDDM have not been identified in most patients. This is due in part to the heterogeneity of the genes responsible for the susceptibility to NIDDM. Obesity is a major risk factor that predisposes one to NIDDM. Genetic studies in mice and rats have demonstrated a link between genes responsible for obesity and those that cause diabetes mellitus.

Pathophysiology of NIDDM

Unlike patients with IDDM, those with NIDDM have detectable levels of circulating insulin. On the basis of oral glucose tolerance testing the essential

elements of NIDDM can be divided into 4 distinct groups; those with normal glucose tolerance, chemical diabetes (called impaired glucose tolerance), diabetes with minimal fasting hyperglycaemia (fasting plasma glucose <140 mg/dL), and diabetes mellitus in association with overt fasting hyperglycemia (fasting plasma glucose >140 mg/dL). In patients with the highest levels of plasma insulin (impaired glucose tolerance group) there was also elevated plasma glucose. This indicates that these individuals are resistant to the action of insulin. In the progression from impaired glucose tolerance to diabetes mellitus the level of insulin declines indicating that patients with NIDDM have decreased insulin secretion.

Additional studies have subsequently demonstrated that both insulin resistance and insulin deficiency is common in the average NIDDM patient. Many experts conclude that **insulin resistance** is the primary cause of NIDDM, however, others contend that **insulin deficiency** is the primary cause because a moderate degree of insulin resistance is not sufficient to cause NIDDM. As indicated above, most patients with the common form of NIDDM have both defects.

A number of candidate genes have been screened for having causative roles in type 2 diabetes. Although several monogenic loci are associated with type 2 diabetes (see MODY descriptions above) none has been shown to be a significant cause of the disease (i.e. >50% in all cases). Several of the genes having roles in progression to type 2 diabetes include pancreatic glucokinase (MODY 2), GLUT-2 (glucose transporter), glucagon receptor, glucagon-like protein-1 (GLIP-1), glucokinase regulatory protein and hexokinase-1.

Recent evidence has demonstrated a role for a member of the nuclear hormone receptor superfamily of proteins in the etiology of type 2 diabetes. A relatively new class of drugs used to increase the sensitivity of the body to insulin are the thiazolidinedione drugs. These compounds bind to and alter the function of the peroxisome proliferator-activated receptor g, PPARg. PPARg is also a transcription factor and, when activated, binds to another transcription factor known as the retinoid X receptor, RXR. When these two proteins are complexed a specific set of genes becomes activated. PPARg is a key regulator of adipocyte differentiation; it can induce the differentiation of fibroblasts or other undifferentiated cells into mature fat cells. PPARg is also involved in the synthesis of biologically active compounds from vascular endothelial cells and immune cells.

Mutations in the gene for PPARg have been correlated with insulin resistance. It is still not completely clear how impaired PPARg signaling can affect the

sensitivity of the body to insulin or indeed if the observed mutations are a direct or indirect cause of the symptoms of insulin resistance.

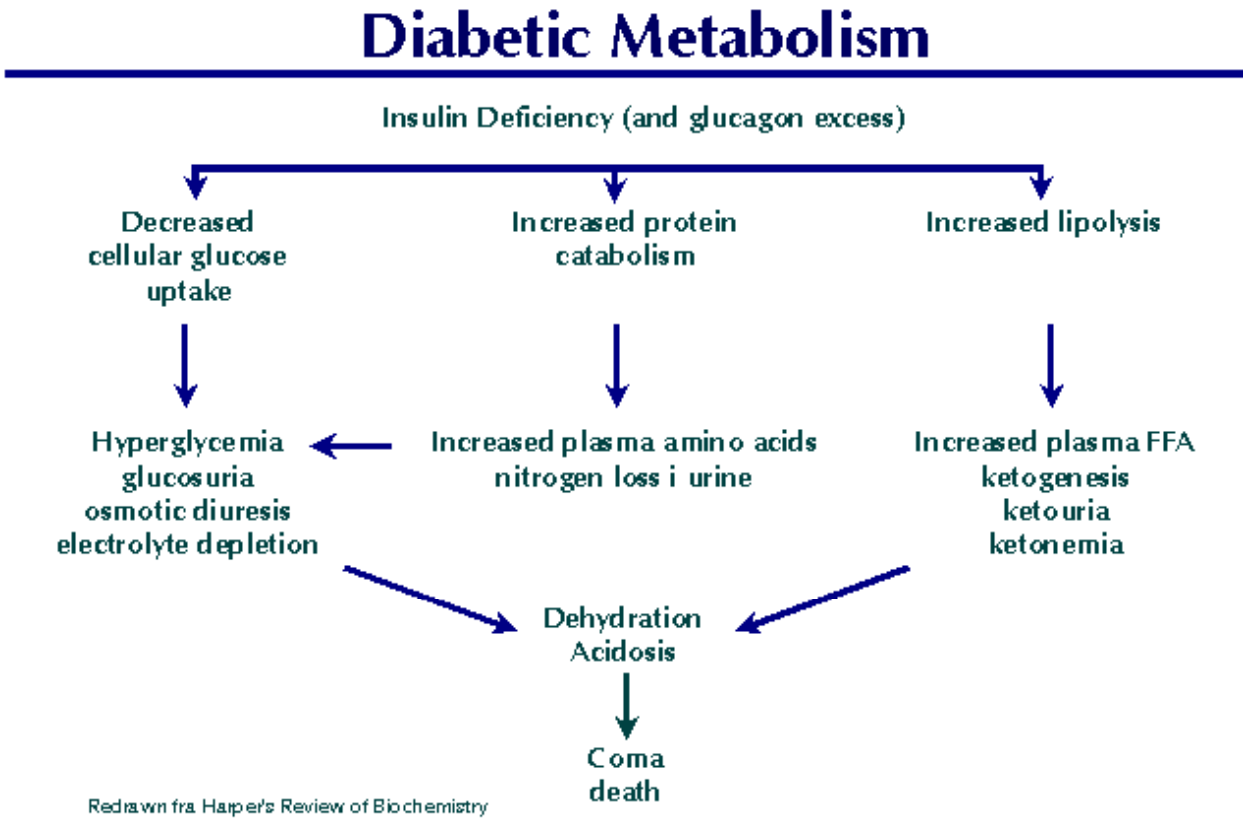
Insulin resistance

Insulin resistance (IR) is a condition in which the cells of the body become resistant to the effects of insulin, that is, the normal response to a given amount of insulin is reduced. As a result, higher levels of insulin are needed in order for insulin to have its effects. The resistance is seen with both the body's own insulin (endogenous) and if insulin is given through injection (exogenous).

The causes of insulin resistance

There are probably several causes of insulin resistance and there is thought to be a strong genetic factor (an inherited component), Some medications also can lead to insulin resistance. In addition, insulin resistance is seen often in the following conditions:

1. the metabolic syndrome
2. obesity
3. Pregnancy
4. infection or severe illness
5. Stress
6. during steroid use



A summary of metabolism in the diabetic state can be seen in the next figure. Note that this figure applies both to uncontrolled diabetes type I and severe uncontrolled diabetes type II.

METABOLIC SYNDROME

An association between certain metabolic disorders and cardiovascular disease has been known since the 1940s. In the 1980s this association became more clearly defined and the term metabolic syndrome (also known as syndrome X or the dysmetabolic syndrome) was coined to designate a cluster of metabolic risk factors that come together in a single individual. In more current times, the term metabolic syndrome is found throughout medical literature and in the lay press as well. There are slight differences in the criteria of diagnosis - depending on which authority is quoted. Regardless, the concept of a clustering of risks leading to cardiovascular disease is well accepted.

The main features of metabolic syndrome include insulin resistance,

hypertension (high blood pressure), cholesterol abnormalities, and an increased risk for clotting. Patients are most often overweight or obese.

Insulin resistance refers to the diminished ability of cells to respond to the action of insulin in promoting the transport of the sugar glucose, from blood into muscles and other

Definition of metabolic syndrome

The definition of metabolic syndrome depends on which group of experts is doing the defining. Based on the guidelines from the 2001 National Cholesterol Education Program Adult Treatment Panel (ATP III), any three of the following traits in the same individual meet the criteria for the metabolic syndrome:

1. **Abdominal obesity:** a waist circumference over 102 cm (40 in) in men and over 88 cm (35 inches) in women.

2. **Serum triglycerides** 150 mg/dl or above.

3. **HDL cholesterol** 40mg/dl or lower in men and 50mg/dl or lower in women.

4. **Blood pressure** of 130/85 or more.

5. **Fasting blood glucose** of 110 mg/dl or above. (Some groups say 100mg/dl)

The **World Health Organization** (WHO) has slightly different criteria for the metabolic syndrome:

A. High insulin levels, an elevated fasting blood glucose or an elevated post meal glucose alone with at least 2 of the following criteria:

- Abdominal obesity as defined by a waist to hip ratio of greater than 0.9, a body mass index of at least 30 kg/m2 or a waist measurement over 37 inches.

B. Cholesterol panel showing a triglyceride level of at least 150 mg/dl or an HDL cholesterol lower than 35 mg/dl.

C. Blood pressure of 140/90 or above (or on treatment for high blood

pressure)

How common metabolic syndrome is.

Metabolic syndrome is quite common. Approximately 20-30% of the population in industrialized countries have metabolic syndrome. By the year 2010, the metabolic syndrome is expected to affect 50-75 million people in the US alone.

The causes of metabolic syndrome

As is true with many medical conditions, genetics and the environment both play important roles in the development of the metabolic syndrome.

Genetic factors influence each individual component of the syndrome, and the syndrome itself. A family history that includes type 2 diabetes, hypertension, and early heart disease greatly increases the chance that an individual will develop the metabolic syndrome.

Environmental issues such as low activity level, sedentary lifestyle, and progressive weight gain also contribute significantly to the risk of developing the metabolic syndrome.

Metabolic syndrome is present in about 5% of people with normal body weight, 22% of those who are overweight and 60% of those considered obese. Adults who continue to gain 5 or more pounds per year raise their risk of developing metabolic syndrome by up to 45%.

While obesity itself is likely the greatest risk factor, others factors of concern include:

- women who are post-menopausal,
- smoking,
- eating an excessively high carbohydrate diet,
- lack of activity (even without weight change), and
- consuming an alcohol-free diet.

Importance of knowing about metabolic syndrome

Metabolic syndrome is worth caring about because it is a condition that can pave the way to both diabetes and heart disease, two of the most common and important chronic diseases today.

Metabolic syndrome increases the risk of type 2 diabetes (the common type of diabetes) anywhere from 9-30 times over the normal population. That's a huge increase. As to the risk of heart disease, studies vary, but the metabolic syndrome appears to increase the risk 2-4 times that of the normal population.

There are other concerns as well that should be mentioned. Metabolic syndrome is associated with fat accumulation in the liver (fatty liver), resulting in inflammation and the potential for cirrhosis. The kidneys can also be affected, as there is an association with microalbuminuria -- the leaking of protein into the urine, a subtle but clear indication of kidney damage.

Other problems associated with metabolic syndrome include obstructive sleep apnea, polycystic menopausal syndrome , increased risk of dementia with aging, and cognitive decline in the elderly.

Treatment

The major goals are to treat both the underlying cause of the syndrome, and also to treat the cardiovascular risk factors if they persist. As has been discussed, the majority of people with metabolic syndrome are overweight and lead a sedentary lifestyle.

Lifestyle modification is the preferred treatment of metabolic syndrome. Weight reduction usually requires a specifically tailored multifaceted program that includes diet and exercise. Sometimes medications may be useful.

Physical activity and exercise help burn calories. The amount of calories burned depends on the type, duration, and intensity of the activity. It also depends on the weight of the person. A 200-pound person will burn more calories running 1 mile than a 120-pound person, because the work of carrying those extra 80 pounds

must be factored in. But exercise as a treatment for obesity is most effective when combined with a diet weight-loss program. Exercise alone without diet will have a limited effect on weight because one has to exercise a lot to simply lose one pound. However regular exercise is an important part of a healthy lifestyle to maintain a healthy weight for the long term. Another advantage of regular exercise as part of a weight-loss program is a greater loss of body fat versus lean muscle compared to those who diet alone.

Other benefits of exercise include:

- Improved blood sugar control and increased insulin sensitivity (decreased insulin resistance)
- Reduced triglyceride levels and increased good HDL cholesterol levels
- Lowered blood pressure
- A reduction in abdominal fat
- Reduced risk of heart disease. A study performed in men found those with moderate activity had a 23 percent lower risk of death than those who were less active.

DIABETES SYMPTOMS

The early symptoms of untreated diabetes are related to elevated blood sugar levels, and loss of glucose in the urine. High amounts of glucose in the urine can cause increased urine output and lead to dehydration. Dehydration causes increased thirst and water consumption. The inability of insulin to perform normally has effects on protein, fat and carbohydrate metabolism. Insulin is an anabolic hormone, that is, one that encourages storage of fat and protein. A relative or absolute insulin deficiency eventually leads to weight loss despite an increase in appetite. Some untreated diabetes patients also complain of fatigue, nausea and vomiting. Patients with diabetes are prone to developing infections of the bladder, skin, and vaginal areas. Fluctuations in blood glucose levels can lead to blurred vision. Extremely elevated glucose levels can lead to lethargy and coma.

Type 1 Diabetes Symptoms

The symptoms of Type I diabetes often come on suddenly and very severely. They include:

- being exceptionally thirsty
- dry mouth
- the need to urinate often
- weight loss (even though you may be hungry and eating well)
- feeling weak and tired
- blurry vision

Type 2 Diabetes Symptoms

Sometimes, people with Type II diabetes don't notice any symptoms or the symptoms are experienced gradually. They include:

- blurry vision
- cuts or sores that are slow to heal
- itchy skin, yeast infections
- increased thirst
- dry mouth
- need to urinate often
- leg pain

Diabetes diagnosis

There are special tests in diagnosing diabetes and also in monitoring blood sugar level control in known diabetics.

If the patient is having symptoms but is not known to have diabetes, the evaluation should always begin with a thorough medical interview and physical examination. The health care provider asks about the symptoms, risk factors for diabetes, past medical problems, medications the patient is taking, allergies to medications, family history of diabetes or other medical problems such as high cholesterol or heart disease, and habits and lifestyle.

A number of lab tests are available to confirm the diagnosis of diabetes.

Fingerstick blood glucose: This is a rapid screening test that may be performed at a medical office or at a hospital emergency department.

- A fingerstick blood glucose test is not as accurate as testing the blood in the

laboratory but is easy to perform, and the result is available right away.

- The test involves sticking the finger for a blood sample, which is then placed on a strip. The strip goes into a machine that reads the blood sugar level. These machines (GLUCOMETERS) are only accurate to within about 10% of actual laboratory values.

- Fingerstick blood glucose values may be inaccurate at very high or very low levels, so this test is only a preliminary screening study. This is the way most diabetics monitor their blood sugar levels at home.

Fasting plasma glucose: The patient should not eat or drink nothing for 8 hours before blood drawn (usually first thing in the morning). If the blood glucose level is greater than or equal to 126 mg/dL without eating anything, probably diabetes exists.

- If the result is abnormal, the fasting plasma glucose test may be repeated on a different day to confirm the result, or the patient may undergo an oral glucose tolerance test or a glycosylated hemoglobin test (often nicknamed "hemoglobin A1c") as a confirmatory test.

- If fasting plasma glucose level is greater than 100 but less than 126 mg/dL, it is called impaired fasting glucose or IFG. This is a prediabetes condition. The patient is at high risk of developing diabetes in the near future.

Oral glucose tolerance test (Stryer pg.780) : This test involves drawing blood for a fasting plasma glucose test and then drawing blood for a second test 2 hours after the patient drinks a very sweet drink containing 75 grams of sugar.

- If the blood sugar level after the sugar drink is greater than or equal to 200 mg/dL, the patient is probably diabetic.

- If the blood glucose level is between 140 and 199, then the patient probably has impaired glucose tolerance, which is also a prediabetic condition.

Glycosylated hemoglobin or hemoglobin A1c: This test is a measurement of how high blood sugar level has been over about the last **120 days**—the lifespan of a red

blood cell.

- Excess blood glucose hooks on to the hemoglobin in red blood cells and stays there for the life of the red blood cell, which is approximately 90 days.

- The percentage of hemoglobin that has had excess blood sugar attached to it can be measured in the blood. The test involves having a small amount of blood drawn.

- A hemoglobin A1c test is the **best measurement** of blood sugar control in people known to have diabetes. A hemoglobin A1c result of 7% or less is considered to indicate good glucose control. A result of 8% or greater is considered to indicate that blood sugar level is too high too much of the time.

- The hemoglobin A1c test is also beginning to be used as a diagnostic test for diabetes. A hemoglobin A1c result greater than 6.1% is highly suggestive of diabetes. Generally, a confirmatory test would be needed before diagnosing diabetes.

- The hemoglobin A1c test is generally measured about **every 3-6 months** for people with known diabetes, although it may be done more frequently for people who are having difficulty achieving and maintaining good blood sugar control.

- This test is not used for people who do not have diabetes or are not at increased risk of diabetes.

- Normal values may vary from lab to lab, although an effort is under way to standardize how measurements are performed.

Diagnosing complications of diabetes (Cecyl pg. 584)

A diabetic patient should be checked regularly for early signs of diabetes complications.

- Eyes should be checked at least once a year by an eye specialist

(ophthalmologist) to screen for **diabetic retinopathy**, a leading cause of blindness.

- Urine should be checked for protein (microalbumin) on a regular basis, at least 1-2 times per year. Protein in the urine is an early sign of **diabetic nephropathy**, a leading cause of kidney failure.

- Sensation in legs should be checked regularly using a tuning fork or a monofilament device. **Diabetic neuropathy** is a leading cause in diabetic lower extremity ulcers, which frequently lead to amputation of the feet or legs.

- Feet and lower legs should be checked at every visit for cuts, scrapes, blisters, or other lesions that could become infected.

- Screen regularly for conditions that may contribute to heart disease, such as high blood pressure and high cholesterol.

RISK FACTORS

TYPE 1

Type 1 can occur at any age but usually appears between infancy and the late 30s, most typically in childhood or adolescence. Boys and girls are equally vulnerable. Studies report the following may be risk factors for developing type 1 diabetes:

- Being ill in early infancy.
- Early foods. Some studies have reported that early exposure to cow's milk in infancy and not being breast fed increased the risk for type 1 diabetes. Studies suggest that very early exposure to cereal--not cow's milk--play a role in risk. Any risk from early dietary factors is still very low and likely to affect children who already have a genetically impaired immune response to dietary proteins. Breast milk contains factors that may help regulate the immune response and prevent diabetes in such children. National differences in risk also suggest that not all cow's milk is the same, and some proteins

may confer higher risks than others.

- Having an older mother.
- Having a mother with type 1 diabetes.
- Having a mother who had preeclampsia during pregnancy.
- Obesity in children has long been linked to a higher risk for type 2 diabetes. Studies reported an association between high weight at birth and obesity during childhood as risk factors for type 1 diabetes as well. The common risk factor may be an increase in insulin secretion, which occurs with obesity. This theoretically could overstress the beta cells so that they become susceptible to damage by overactive immune factors (particularly cytokines), and eventually destruction in children genetically vulnerable to type 1 diabetes.

Until recently, diabetes in children was almost always type 1 diabetes. Of major concern, however, are estimates that between 8% and 45% of new diabetes cases in children are now type 2, most likely because of the increase in childhood obesity.

Having Other Immune Abnormalities

The incidence of type 1 is higher than average among people with other autoimmune diseases, including Grave's disease, Hashimoto's thyroiditis (a form of hypothyroidism), Addison's disease, multiple sclerosis (MS), and pernicious anemia. Research, in fact, has raised the possibility that all autoimmune diseases share a common genetic basis; for example, the T-cell immune factors in type 1 diabetes target the same self-antigens as in multiple sclerosis (MS). And both diseases have been associated with cow's milk protein. Many questions are unanswered, however. It is not known why the diseases develop in different locations to cause separate disorders or why some autoimmune events occur in everyone but not everyone develops an autoimmune disease.

Ethnicity

There is a very wide variation in incidence of type 1 among population groups. Type 1 diabetes appears to be most common in people of northern European descent and in specific Mediterranean groups (such as Sardinians). It is less common among Asians and African Americans. Still, African Americans with type 1 diabetes are 50% more likely to die from it than Caucasians are, mostly due to lower-quality health care.

TYPE 2

The more risk factors an individual has, the greater his/her likelihood of developing type 2 diabetes. Individuals with any of the risk factors should talk to a health professional about how to lower their risk, and discuss whether testing is needed.

Obesity

An excessively high body weight increases diabetes risk. The Body Mass Index(BMI) is a simple, widely accepted means of assessing body weight in relation to health for most people aged 20 to 65 (Exceptions include people who are very muscular, athletes, pregnant or nursing). A BMI greater than 27 indicates a risk for developing type 2 diabetes, and other health problems which include cardiovascular disease, and premature death. The implications of the BMI are not the same for everyone.

Apple-shaped figure

Individuals who carry most of their weight in the trunk of their bodies (i.e., above the hips) tend to have a higher risk of diabetes than those of similar weight with a pear-shaped body (excess fat carried mainly in the hips and thighs). A waist measurement of more than 100 cm (39.5 inches) in men and 95 cm (37.5 inches) in women suggests an increased risk.

Age

Age increases the risk of type 2 diabetes. Prevalence rate of diabetes in those aged 65 and over (10.4%) is three times as high as the rate in those 35 to 64 (3.2%).
While most diabetes occurs in older persons, it should be noted that the appearance of type 2 diabetes in children is increasingly being reported in the medical literature.

Sedentary lifestyle

Being overweight - another risk factor for Type 2 - can be prevented by regular physical activity. A second, independent benefit of regular physical activity is improved blood sugar control in persons who already have type 2 diabetes.

Family History

The genetic link for type 2 diabetes is stronger than the genetic link for type 1. Having a blood relative with type 2 diabetes increases the risk. If that person is a first-degree relative (e.g., a parent, sibling or child), the risk is even higher.

History of Diabetes in Pregnancy

Nearly 40 percent of the women who have diabetes during their pregnancy go on to develop type 2 diabetes later, usually within five to ten years of giving birth. Giving birth to a baby that weighs more than nine 4 kg is another symptom of gestational diabetes.

Impaired Glucose Tolerance

Impaired glucose tolerance or impaired fasting glucose can precede the development of type 2 diabetes. While persons affected with these problems do not meet the diagnostic criteria for diabetes, their blood sugar control and reaction to sugar loads are considered to be abnormal. This places them at higher risk, not just for the development of type 2 diabetes (an estimated one in ten progress to type 2 diabetes within five years), but also for cardiovascular disease. For this group, preventive strategies, including lifestyle changes and regular screening for diabetes mellitus, must be a priority.

Ethnic Ancestry

Being of Aboriginal, African, Latin American or Asian ethnic ancestry increases the risk of developing of type 2 diabetes. Risk levels for these groups are between two and six times higher than for Canadians of Caucasian origin.

High Blood Pressure

Up to 60 percent of people with undiagnosed diabetes have high blood pressure.

High Cholesterol or other fats in the blood

More than 40 percent of people with diabetes have abnormal levels of cholesterol and similar fatty substances that circulate in the blood. These abnormalities appear to be associated with an increased risk of cardiovascular disease among persons with diabetes.

COMPLICATIONS OR SEQUELAE OF DIABETES

Sometimes a complication of diabetes may give a clue to the presence of the disease. The principle complications or sequelae associated with diabetes are **retinopathy**, **neuropathy**, **nephropathy** and **arteriosclerosis**. Whether these are the unavoidable consequences of the diabetic state over time or whether they may be influenced by controlling the diabetes through aggressive monitoring, treatment and life-style management, including diet and supplements, remains a central topic.

Studies have shown that keeping blood sugar levels as close to normal as possible through aggressive management slows the onset and progression of eye, kidney and nerve diseases caused by diabetes, even if the person has a history of poor control. Specifically it found that lowering and maintaining more constant blood sugar levels reduced the risk of eye disease by 76%, kidney disease by 50%, nerve disease by 60% and cardiovascular disease by 35%.

Since the discovery of insulin nearly 70 years ago, the patterns of morbidity from diabetes have changed. Where the major causes of death were ketoacidosis and infection, they are now the microvascular and cardiovascular complications of diabetes (renal failure and myocardial infarction).

These complications are responsible for a reduction in the life expectancy of a newly diagnosed insulin dependent diabetic by about one-third. The basis of managing diabetes in the 90's is an improvement in the life-style of the diabetic and prevention of complications responsible for morbidity and mortality in diabetes.

Neuropathy (nerve disease) (Cecyl pg.596)

Diabetic neuropathies are among the most frequent complication of long-term diabetes. It is estimated that 60% to 70% of diabetics have mild to severe forms of nervous system damage. The femoral nerve is commonly involved giving rise to symptoms in the legs and feet. Pain is the chief symptom and tends to worsen at night when the person is at rest. It is usually relieved by activity and aggravated by cold. Paraesthesias are a common accompaniment of the pain. Cramping, tenderness and muscle weakness also occur but atrophy is rare. Advanced femoral nerve disease is a major contributing cause of lower extremity amputations. Nerves in the arms, abdomen and back may also be affected. Symptoms may include impaired heart function, slowed digestion, reduced or absent perspiration, severe

oedema, carpal tunnel syndrome, alternating bouts of diarrhoea and constipation, bladder atony, urinary and faecal incontinence and impotence.

With respect to sexual impotence, diabetes is probably the single most common disease associated with erectile failure (termed neurogenic impotence in the diabetic). Since diabetes is a metabolic disease with vascular and nervous system complications and an erection involves all levels of the nervous system from the brain to the peripheral nerves, lesions anywhere along the path may be responsible for erectile failure. It has been estimated that close to 50% of diabetic males have some degree of erectile dysfunction. Neuropathies usually improve with the control of the diabetes. Severe or chronic changes may require several weeks or months to show maximum improvement.

Retinopathy (eye disease) (Cecyl pg.596)

Changes occurring in the eye which are distinctive of diabetes involve the narrowing, hardening, bulging, haemorrhaging or severing of the veins and capillaries of the retina. This is a serious complication known as retinopathy and may lead to loss of vision. Visual changes in the earlier stages may include diminished vision, contraction of the visual field, changes in the size of objects or photophobia. In the more advanced stage, termed 'proliferative retinopathy', haemorrhages, retinal detachment and other serious forms of deterioration are observed. When the disease progresses to this late stage total blindness may occur.

It usually takes between 10-13 years for diabetic retinopathy to develop and it is present in some degree in most diabetics who have had the disease for 20 years. In only about half of the diabetics who develop it however, is vision markedly impaired and blindness occurs in only about 6%. Still, diabetes is the leading cause of blindness in adults 20 to 74 years old and is estimated to cause from 12,000 to 24,000 new cases each year. Two other complications of diabetes, cataracts and glaucoma, can also lead to loss of vision

The development of laser therapy will probably reduce the prevalence of diabetes-induced blindness, however this therapy is not without occasional side effects (haemorrhage, retinal detachment and loss of visual field) and is therefore indicated only for the more serious conditions.

Arteriosclerosis (vessel disease)

The diabetic state is associated with earlier and more severe vascular changes than normally occur at a given age. Cardiovascular-renal disease is the leading cause of death among diabetics. Atherosclerosis can be accurately described as the end stage of Type 1 and Type 2 diabetes, since the vast majority of diabetes patients will die from an atherosclerotic event. Most commonly these events are cardiovascular in nature (an estimated 60% to 65% of diabetics have high blood pressure) although 20-25% of atherosclerotic events may be cerebrovascular or microvascular.

The incidence of coronary occlusion in persons with clinical diabetes has been estimated at from 8-17% with diabetic adults having heart disease death rates about 2 to 4 times as high as the general population. The risk of stroke is also found to be 2 to 4 times higher in people with diabetes. Arteriosclerosis obliterans in the lower extremities (diabetic foot), a form of peripheral vascular disease, may produce disturbances in sensation, decrease in muscular endurance, intermittent claudication on effort, absence of peripheral pulses in the lower legs and feet and gangrene, and ultimately lead to amputation of the extremity. Diabetic gangrene usually involves the toes, heels or other prominent parts of the feet and is precipitated by trauma, infection or extremes in temperature. Needless to say, careful attention to proper foot care, avoidance of injury and consistent use of methods to improve peripheral circulation, including withdrawal from tobacco use in any form, are critical for the diabetic. The aetiology of large vessel disease is multi-factorial in the diabetic as well as the non-diabetic population with lipoprotein metabolism, hypertension, physical activity, obesity, cigarette smoking, stress, personality and genetic and racial factors all playing a part.

Nephropathy (kidney disease) (Cecyl pg.597)

Nephropathy is a common and important accompaniment of diabetes and one that in young diabetics takes precedence over heart disease as a cause of illness and death. As with eye changes, there is a wide variation in the type and degree of renal damage. Nephropathy is less frequent than retinopathy and where it occurs is also a development of long standing diabetes.

One study reported that among 200 juvenile diabetics who survived 20 years after onset, one half had evidence of renal disease. Another study found that the majority of these patients have hypertension and two thirds show significant albuminuria, but the fully developed nephrotic syndrome of hypertension,

proteinuria and oedema occurs in less than 10% and renal function is impaired in only one half to three quarters of those patients.

Like other long-term complications, good blood glucose control goes a long way towards reducing the risk of diabetic nephropathy. In addition to monitoring the blood sugar levels, periodic monitoring of a diabetic patient's kidney function (blood urea nitrogen, uric acid, creatinine and creatinine clearance) is important.

Hypoglycaemia

If there is too much insulin in the body compared to the amount of blood sugar, and the blood sugar falls below normal levels, a condition known as hypoglycaemia occurs. This problem of hypoglycaemia due to insulin or oral hypoglycaemic drugs is much more common in Type 1 than Type 2 diabetes since the Type 1 diabetic is directly injecting insulin. If too much insulin is administered, or the person misses a meal or over-exercises, hypoglycaemia may result. In this condition, commonly referred to as insulin shock, the brain is deprived of an essential energy source. The first sign is mild hunger, quickly followed by dizziness, sweating, palpitations, mental confusion and eventual loss of consciousness. Before the condition reaches emergency proportions, most diabetics learn to counteract the symptoms by eating a sweet or drinking a glass of orange juice. Blood glucose chewing tablets are also available in pharmacies. In some cases, the only effective measure is an intravenous injection of glucose.

Digestive Disorders

Diabetics are more likely than the general population to report a number of digestive conditions, including ulcers, diverticulitis, symptoms of irritable bowel syndrome, abdominal pain, constipation, diarrhoea and gallstones.

Oral Complications

Periodontal disease, which can lead to tooth loss, occurs with greater frequency and severity among diabetics. Periodontal disease has been reported to occur among 30% of people aged 19 years or older with Type1 diabetes.

Infections

Studies in clinic, community and hospital populations indicate that diabetic

subjects have a higher risk of some infections, including asymptomatic bacteriuria, lower extremity infections, re-activation tuberculosis, infections in surgical wounds and group B streptococcal infection. Populationbased data suggest a probable higher mortality from influenza and pneumonia.

Complications of Pregnancy

The rate of major congenital malformations in babies born to women with pre-existing diabetes varies from 0% to 5% among women who receive preconception care, to 10% among women who do not receive preconception care. Between 3% to 5% of pregnancies among women with diabetes result in death of the new-born; the rate for women who do not have diabetes is 1.5%4.

Ketoacidosis

Another acute complication more likely to occur in the IDDM is diabetic ketoacidosis which can directly cause an acute life-threatening event, a diabetic coma.

The possibility of ketoacidosis is suggested by:

- Confusion or coma, the patient almost always appearing extremely ill.
- Air hunger - an attempt to compensate for metabolic acidosis.
- Acetone odor (fruity) invariably on the breath.
- Nausea and vomiting almost always present.
- Abdominal tenderness which may mimic viral gastroenteritis.
- Extreme thirst and dry mucous membranes.
- Diabetic history (present in about 90% of cases).
- Weight loss.

Before the discovery of proper treatment by insulin and other intravenous injections, acidosis was the chief cause of death among diabetics. Today diabetics can use a simple urine dipstick at home to measure the level of ketones (excreted ketoacids) in the urine.

Diabetic nutrition

Any food that is high in any type of carbohydrate will raise blood glucose levels soon after a meal. Whether a food contains one ounce of sugar (natural or refined) or one ounce of starch, it will raise blood glucose the same amount, because the

total amount of carbohydrate is the same. Although a glass of fruit juice and the same amount of sugary soda may seem like a "good" versus "bad" choice, each will raise blood glucose about the same amount. This information regarding the amount of carbohydrate in different foods is the center of a nutrition management tool for people with diabetes called Carbohydrate Counting. Foods high in carbohydrates include starches such as rice, pasta, breads, cereals, and similar foods; fruits and juices; vegetables; milk and milk products; and anything made with added sugars, such as candies, cookies, cakes, and pies.

The goal of a diabetes nutrition plan is to provide a mixture of fats, carbohydrates, and proteins at each meal at an appropriate calorie level to both provide essential nutrients as well as create an even release of glucose into the blood from meal to meal and from day to day. A Registered Dietitian assesses the nutritional needs of a person with diabetes and calculates the amounts of fat, protein, carbohydrate, and total calories needed per day, and then converts this information into recommendations for amounts and types of foods to include in the daily diet. The total number of meals and snacks and their timing throughout the day can differ for each person, based on his or her nutritional needs, lifestyle, and the action and timing of medications.

Overall, a nutrition plan for a person with diabetes includes 10 to 20% of calories from protein, no more than 30% of calories from fats (with no more than 10% from saturated fats), and the remaining 50 to 60% from carbohydrates.

Carbohydrate foods that contain dietary fiber are encouraged, as a high fiber diet has been associated with decreased risks of colon and other cancers. For people with high blood cholesterol levels, lower total fat and saturated fat contents may be recommended. Sodium intake of no more than 3000 mg per day is suggested; for people with high blood pressure, sodium should be limited to 2400 mg per day or as advised by a physician.

One "diabetic diet" definitely does not fit all. In fact, any food can fit into the diet of someone with diabetes, with the help and guidance of a Registered Dietitian.

Managing blood glucose levels does not have to mean giving up favorite foods, sweets, or restaurants and fast foods. Each person with diabetes has very different nutritional and personal needs, making ongoing assessment and counseling with a Registered Dietitian an essential element of successful diabetes management.

Although sugar can be part of diet of people with diabetes, sugar substitutes are often used as a way of reducing carbohydrates. Common substitutes in alphabetical

order are:

- Acesulfame-K
- Aspartame
- Fructose
- Isomalt
- Saccharin
- Stevia
- Sucralose
- Sugar Alcohols (ex.Sorbitol)

INSULIN TREATMENT

INSULIN ADMINISTRATION

Many people with diabetes need to take insulin administration-absolute need for **IDDM (TYPE 1)-**to control bood glucose levels. There are many options for administering insulin but the most popular is still the needle and the syringe.

No matter the method of injection, the injection site affects how quickly the medication is absorbed into the body. Patients need to vary their injection sites to prevent damage to tissues.

Insulin is absorbed the most quickly when injected into the abdomen. Other sites often used for injections include the arms, thighs or buttocks. Patients should be sure to choose an injection site that is at least a half-inch away from the site of their previous injection.

Insulin can be delivered:

1. Under the skin (**subcutaneously**). This is the most common way to deliver insulin into the blood stream.
2. Into a vein (**intravenously**). This is the quickest way to deliver insulin into the blood stream.
3. Into the muscle (**intramuscularly**). This is the second quickest way to deliver insulin into the blood stream.
4. By mouth (**orally**). A special inhaler delivers inhaled insulin powder through the mouth and then to the lungs for absorption.Patients injecting insulin should be sure to thoroughly clean the skin at the injection site to prevent infection. Insulin should be delivered at an angle suggested by a physician. This is usually between 45 and 90 degrees and depends on the thickness of a patient's skin.

Special adaptation equipment is available to help people with diabetes with vision or motor difficulties use insulin-delivery devices. Patients should consult their physician to ensure that they are properly administering their medication in a manner that maximizes its potential effectiveness.

Recent research suggests that many diabetic individuals, particularly those not yet prescribed insulin, would risk their health to avoid insulin injections and that some physicians are reluctant to prescribe the medication to patients who would benefit from it.

TYPES OF INSULIN

Type of insulin	Generic and brand names	How long it takes to begin working (onset)	When it has the most effect on your blood sugar (peak)	How long the overall effect lasts (duration)
Rapid-acting (clear sol.) Absorbed more quickly than short-acting insulin, but effects wear off sooner	Insulin aspart (NovoLog) Insulin glulisine (Apidra) Insulin lispro (Humalog)	10 to 30 minutes	30 minutes to 3 hours	3 to 5 hours
Short-acting (clear sol.) Works quickly, but effects don't last as long as intermediate-acting insulin	Insulin regular (Humulin R, Novolin R, others)	30 to 60 minutes	2 to 5 hours	Up to 8 hours
Intermediate-acting Starts working later than short-acting insulin, but effects last longer	Insulin NPH human (Humulin N, Novolin N)	1 to 2 hours	4 to 12 hours	16 to 24 hours
Long-acting Takes several hours to work, but provides insulin at a steady level for up to 24 hours	Insulin glargine (Lantus) Insulin detemir (Levemir)	1 to 5 hours	No clear peak	Up to 24 hours

Short and rapid acting ins. are the only suitable insulin for IV administration
Intermediate-acting:
1. Insulin zinc suspension amorphous-lente.
2. Isophane insulin (NPH): susp. of soluble insulin and protamine.
3. Biphasic insulin: A single vial contains a fixed ratio of insulin (% rapid- or fast-acting to % intermediate-acting insulin; (10% soluble ins.+90% isophane ins.) **to** (90% soluble ins.+10% isophane ins.).

Long-acting
1. Insulin zinc suspension crystalline-untalented
2. Protamine-zinc insulin [1]

INSULIN DELIVERY DEVICES

Needle and syringe

A common way of administering insulin is with a needle and syringe. Syringes come in a range of capacities (1 mL, 0.5 mL or 0.3 mL) and with a range of needle types (different gauges — that is thicknesses — and lengths) attached. The needles have very fine points and special coatings to make injections relatively pain-free. The patient should select the syringe that suits the size of the insulin dose he takes and should have his preferred needle type and needle size attached.
One of the main advantages of the syringe system is the variety of products available. Needles and syringes also make it easy to use a mixture of different types of insulin ('mixed insulin'), and to draw up a week's supply in advance, to be stored in the refrigerator.
However, some people find syringes daunting and not very convenient. For this reason a number of other delivery devices have been developed, including insulin pens, jet injectors and pumps.

Insulin Syringe

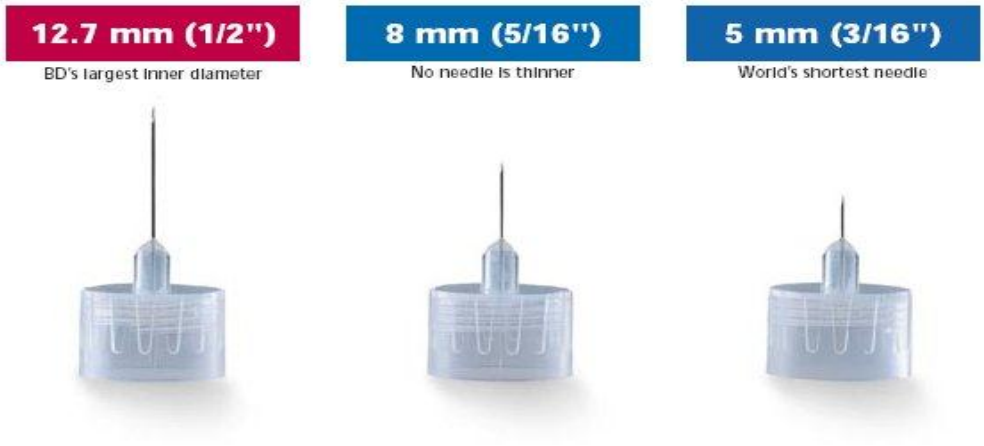
Traditional syringes are still the most common method to deliver insulin.

Insulin pens

Insulin pen injectors are a convenient and discreet way of administering insulin. They have a built-in dial that allows the patient to determine the amount of insulin to be injected, a short needle at one end, and a plunger at the other. Some are disposable, and don't need to be assembled before use, while others have a replaceable insulin cartridge that needs to be inserted (much like a fountain pen cartridge).

Insulin pens are particularly useful if the patient needs to take premixed insulin. They have become popular for use by people with both type 1 or type 2 diabetes.

Insulin pen: Patients turn a dial to set the dosage and press a plunger to deliver the medicine, usually in the abdomen, upper arms, thighs or buttocks. It is important that patients using insulin pens ensure that they properly mix the insulin before injecting the medication. Recent research indicates that many patients are not properly mixing their dosages, which results in insulin that is absorbed too quickly. This increases the chance of episodes of low glucose (hypoglycaemia).

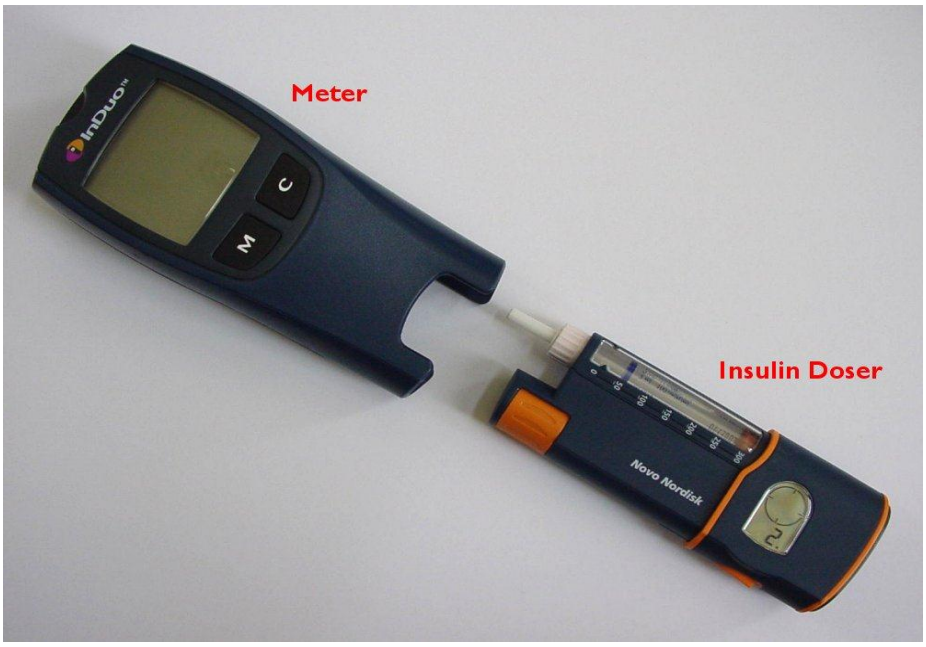


Pen needles

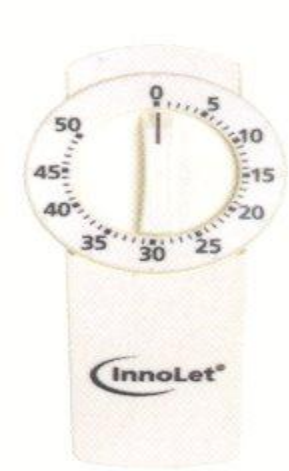
"Pen" Devices in Different Shapes

Pens have traditionally been shaped like a large pen, hence the name. In recent years, new products have been introduced that function like pens; they use insulin cartridges and disposable needles but which are shaped differently. These devices include the Innovo; the InDuo and Innolet .With young kids, half-unit dosing is essential, so these products are better suited for older kids and adults.

Innovo: easy-to-read LCD displays and remember the last dose and how long ago it was delivered, though they can only deliver insulin in increments of one unit.



InDuo: Insulin doser + glucometer +easy-to-read LCD displays for remembering the last dose and how long ago it was delivered, though they can only deliver insulin in increments of one unit.



Innolet; a pre-filled device available with N or 70/30 insulins only; uses a dial, much like a kitchen timer, to set the does and can deliver insulin in one unit increments.

Insulin inhalers

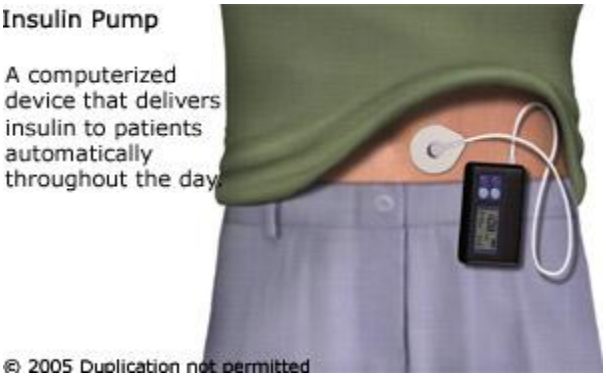
Insulin inhalers are a new way of delivering pre-mealtime insulin. Insulin inhalers work like an asthma inhaler, but deliver dry powdered insulin into the bloodstream via the lungs. However, because the system can only be used to deliver fast-acting insulin, long-acting insulin must still be injected. Large doses are needed because only around 10 per cent of the dose actually reaches the bloodstream and that amount may vary, for instance, if the patient has a cold or asthma. Clinical trials involving about 2,500 people with diabetes have found inhaled insulin (Exubera) to be safe and effective. The FDA approved the medication for adults who have type 1 and type 2 diabetes. Its use in children is still being studied. Some people, especially those with type 1, will still need to inject long-acting insulin. People who smoke, recently quit smoking or have asthma, bronchitis or emphysema are not to use this form of insulin. Annual lung function tests are advised. The American Diabetes Association has expressed optimism that inhaled insulin may increase
compliance but concern that it may have long-term effects on the lungs.

Insulin jet injectors

Jet injectors offer an alternative to needles, and work by sending a fine spray of insulin into the skin using a pressurised jet of air instead of a needle. However, jet injection isn't any less painful than administering insulin with a needle, and may cause bruising or altered absorption levels. Jet injectors also require frequent cleaning and maintenance.

External insulin pumps

External insulin pumps are small devices the size of a pager that can be attached to the belt or placed in the pocket. They run off batteries. They are made up of an insulin reservoir connected to a tube, ending in a cannula or catheter, which is inserted under the skin of the abdomen. They can be set to deliver insulin at a slow, continuous rate throughout the day, or to release larger quantities at meal times or when blood sugar levels are high.
The main advantage of a pump is that it closely mimics the slow but continual release of insulin by the pancreas. However, the patient will still need to monitor your blood glucose levels regularly. Pumps have been useful in helping people with diabetes achieve tighter blood glucose control, but the risk of episodes of low blood sugar (hypoglycaemia) is higher. Another drawback of pumps is the risk of ketoacidosis if the catheter becomes blocked. Expense may also be an issue.



Implantable pumps

Implantable pumps which deliver insulin either intravenously or directly to the liver are currently being tested in people with diabetes (they are not yet available to all countries). They are usually implanted into the left side of the abdomen, and are designed to work in a similar way to external insulin pumps, that is, by giving a continuous 'basal' dose of insulin with the ability to deliver additional 'bolus' doses at meal times. Also under investigation is a version of the pump that measures blood glucose as well, and so delivers the correct insulin dose automatically. However, these devices are complicated and expensive, and can become blocked. If there are complications or infection at the implantation site the pump may have to be removed.

Insulin patches

Insulin patches are also currently under development, but it is difficult for insulin to be absorbed through the skin. The patch is designed to release insulin slowly and continuously. Additional doses can be administered by pulling off a tab on the patch.

Other delivery devices

Insulin sprays, either for the nose or mouth, and oral insulin (insulin pills) are methods of insulin delivery that continue to be investigated. These options represent long-term possibilities for insulin delivery, as difficulties in obtaining adequate amounts of insulin in the bloodstream are yet to be overcome.

Islet cell transplantation

This is a recently developed surgical procedure — called the Edmonton protocol — whereby islet cells from a donated human pancreas are injected into the liver of a recipient with type 1 diabetes. The transplanted cells begin to secrete insulin, while the recipient needs to take immunosuppressive medications for life to prevent rejection of the transplanted tissue. Clinical trials continue to establish the safety and long-term effectiveness of this procedure as a means of supplying insulin.

PERORAL ANTIDIABETICS

1. SULFONYLUREAS

Sulfonylureas, the first drug group introduced in 1955, stimulates the beta cells to produce insulin. Insulin from the beta cells is released directly to the liver via the portal vein, allowing it to work more effectively. These drugs have kept many Type 2 diabetes off injected insulin. Sulfonylureas will not work in those with Type 1 diabetes (except for a specific type) nor in anyone with Type 2 whose beta cells no longer produce insulin. Loss of insulin production, indicated by a low C-peptide level in the blood, is found in those with Type 1diabetes who have Type 1.5 diabetes, and many others with Type 2 diabetes for more than 6 to 15 years.
Mechanism of action

Binding of hypoglycemic sulfonylureas and their analogues to the sulfonylurea receptor in the beta-cell plasma membrane mediates closure of the ATP-sensitive K+-channel (KATP-channel) and thereby stimulation of insulin release. The sulfonylurea receptor is a member of the traffic ATPase family with two intracellular nucleotide binding folds. The receptor binding site for hypoglycemic drugs is located at the cytoplasmic face of the plasma membrane. Mutations in the sulfonylurea receptor gene have been detected which cause familial hyper-insulinism. Non-beta-cell sulfonylurea receptors do not contribute to the therapeutic benefit of sulfonylureas, but might be involved in presumed adverse effects of sulfonylureas in the cardiovascular and the central nervous system.

The original **"first generation"** sulfonylureas include tolbutamide tolazamide, acetohexamide and chlorpropamide. These drugs work well in lowering the blood sugar, but they have a major drawback. Because they bind to proteins in the blood, they can be dislodged by other medications that bind to these same proteins. Once dislodged, their activity can increase rapidly and lead to low blood sugars. Chlorpropamide lasts longer in the blood and on rare occasions can cause a severe and long-lasting form of hypoglycemia. Its use was phased out as newer, safer sulfonylureas became available. [3,5]

Second generation sulfonylureas include glipizide and glyburide. A **third generation** called glimepiride is also available. These drugs have an advantage for those who use other medications since they do not bind to carrier proteins in the blood. Because of this, drug interactions that may cause low blood sugars are less likely. Sulfonylureas work best when taken at the same time each day. Glyburide and glipizide are shorter-acting versions. Glyburide and glipizide are usually taken twice a day, half before breakfast and half before dinner. Sustained-release versions are also available. Long-lasting versions can be taken once a day instead of twice a day. These medications can be used once a day before the evening meal when a person has high blood sugars at bedtime or before breakfast if care is taken to monitor the daytime blood sugar until the safety of the dose is assured. As well as stimulating insulin production, glimepiride may cause a mild reduction in insulin resistance and may be less likely to cause low blood sugars than other sulfonylureas. It is also safer for people who have advanced kidney disease indicated by an elevated creatinine level. Other sulfonylureas are usually not recommended when the creatinine level is elevated. Glimepiride also does not block the normal relaxation of blood vessels and does not affect coronary arteries. These unwanted side effects may occur infrequently with other sulfonylureas.

When starting a sulfonylurea, the risk of a low blood sugar is greatest during the first few days to first four months of use. Careful should be taken during this time and checking of blood sugar often during exercise, increase activity, or skipping of a meal. Drinking alcohol or taking certain medications like decongestants can also increase the risk of a low. Medications, such as steroids, beta blockers and niacin decrease the action of a sulfonylurea and cause the blood sugar to rise. [3,5]

Sulfonylureas

Target Organ: Pancreas

Action: Increase insulin release
Lowers HbA1c by 1% to 2%

Taken: with or without food

Drug	**Acts Over**	**Dose Range**	**Rel.Potency**	**Doses/Day**
Orinase (tolbutamide)	6-10 hrs	500 - 3000 mg	1	2-3
Tolinase (tolazamide)		100 - 1000 mg	3	1-2
Diabinese (chlorpromazine)	24-72 hrs	100 - 500 mg	6	1-2
Glucotrol (glipizide)	12 hrs	2.5 - 40 mg	75	1-2
Glucotrol XL (ext. rel. glipizide)	24 hrs	2.5 - 20 mg	150	1
Micronase, Diabeta (glyburide)	18-24 hrs	1.25 - 2.0 mg	150	1-2
Glynase (micronized gly.)	24 hrs	3 - 12 mg	250	1-2
Amaryl (glimepiride)	24 hrs	1 - 8 mg	350	1

Side Effects: low blood sugar, bloating, nausea, heartburn, anemia, weight gain, sun sensitivity, metallic or change in taste in 1% to 3 %

Contraindications: Type 1 diabetes, advanced liver or kidney disease, sulfa allergy

2. MEGLITINIDES

The meglitinides repaglinide (Prandin) and nateglinide (Starlix) are non-sulfonylurea insulin secretagogues that are both fast acting and of short duration. Like the sulfonylureas, meglitinides therapy results in significant reduction in FPG (**fasting plasma glucose test)** as well as HbA_{1c}. The mechanism of action of the meglitinides is initiated by binding to a receptor on the pancreatic b-cell that is distinct from the receptors for the sulfonylureas. However, meglitinides do exert effects on potassium conductance. Like the sulfonylureas, the meglitinides have no direct effects on the circulating levels of plasma lipids.

Two drugs in this class are now available – Prandin, derived from benzoic acid and approved by the FDA in 1997, and Starlix, derived from D-phenylalanine and approved in 2000. They enhance insulin release from the pancreas over a short period of time only when the glucose level is high. Therefore, the risk of hypoglycemia is reduced. Their activity more closely mimics normal first phase insulin release when food is eaten by a person without diabetes. Peak activity is seen in one hour and the short action time of three hours makes them ideal for matching carbohydrates in meals.

Prandin or Starlix are taken 10 to 15 minutes before meals and do not need to be taken if a meal is skipped. Like sulfonylureas, they do not work in Type 1 diabetes and work in Type 1.5 and Type 2 only as long as the beta cells are capable of producing insulin.

People who eat carbohydrates and then have their blood sugars spike more than 40 or 50 mg/dl above their pre meal readings are the most likely to benefit from these drugs. However, most people do not check to see how high their blood sugar is spiking after eating. Testing at one or two hours after a meal is of real value because it can identify those who may benefit from one of these drugs. One minor inconvenience of the drug is the need to remember to take it several times a day before meals.

In people who retain residual insulin production, one of these medications can be combined with a basal insulin like NPH, Detemir, or Lantus to provide great control. The injected insulin provides basal coverage to keep the fasting blood sugar at a good level, while one of the rapid insulin releasers can enhance internal insulin release to control the blood sugar after meals.

Interactions with other drugs may occur. Certain drugs may increase the effect of these medications, including large doses of aspirin, sulfonamides, chloramphenicol, coumarins, monoamine oxidase inhibitors, and probenecid. Drugs that may decrease their effect include calcium channel blockers, corticosteroids, oral contraceptives, thiazide diuretics, thyroid preparations, estrogens, phenothiazines, phenytoin, rifampin, isoniazid, phenobarbital, and sympathomimetics. One advantage to the medications is that they can be taken safely by people with impaired kidney function or sulfa allergies. [5]

Megitinides-Rapid Insulin Releasers

Target Organ: pancreas

Action: Increases first phase insulin release, glucose driven, lowers after-meal glucose

Lowers HbA1c by 0.5% to 2.0%

Time to reach maximum effect: 1 hr

Taken: Starlix is taken right before each meal while Prandin is taken 15 - 30 minutes before each meal

Drug	**Acts**	**OverDose Range**	**Doses/Day**
Prandin (repaglinide) before each meal	3 hrs	2 - 3	0.5 - 4 mg
Starlix (nateglinide) before each meal	3 hrs	2 - 3	60 - 120 mg

Side Effects: low blood sugar, nausea, vomiting, diarrhea, muscle aches, upper respiratory infection, cold and flu like symptoms, headache, joint aches, and back pain

Contraindications: Type 1 diabetes, liver disease

3. BIGUANIDES

The biguanides are a class of drugs that function to lower serum glucose levels by enhancing insulin-mediated suppression of hepatic glucose production and enhancing insulin-stimulated glucose uptake by skeletal muscle.

Two drugs from the biguanide class, **metformin** and **phenformin**, were developed in 1957. Unfortunately, phenformin reached the market first and resulted in several deaths from lactic acidosis. When this risk surfaced, phenformin was pulled from drugstore shelves worldwide. Metformin was eventually found to be 20 times less likely to cause lactic acidosis, but it was tainted by the history of its cousin. Metformin first became available in France in 1979 and has been widely used in Europe since then, but it was not cleared for use in Type 2 diabetes in the U.S. until 1994. Metformin is a chemical kin to the French lilac plant (of the genus Syringa), which was noted in the early 1900's to lower the blood sugar. However, French lilac, like phenformin, turned out to be too toxic for use in humans.

Metformin is currently the most widely prescribed insulin-sensitizing drug in current clinical use. Metformin administration does not lead to increased insulin release from the pancreas and as such the risk of hypoglycemia is minimal. Because the major site of action for metformin is the liver its use can be contraindicated in patients with liver dysfunction. The drug is ideal for obese patients and for younger type 2 diabetics.

Evidence on the **mode of action** of metformin shows that it improves insulin sensitivity by increasing insulin receptor tyrosine kinase activity, enhancing glycogen synthesis and increasing recruitment and transport of GLUT4 transporters to the plasma membrane. Additionally, it has been shown that metformin affects mitochondrial activities dependent upon the model system studied. Metformin has a mild inhibitory effect on complex I of oxidative phosphorylation, has antioxidant properties, and activates both glucose 6-phosphate dehydrogenase (G6PD) and AMP-activated protein kinase (AMPK). The importance of AMPK in the actions of metformin stems from the role of AMPK in the regulation of both lipid and carbohydrate. In adipose tissue, metformin inhibits lipolysis while enhancing re-esterification of fatty acids.

Metformin, with a much shorter action time than phenformin, has a much lower

risk for severe side effects and is quite safe for use by anyone who is otherwise healthy. In fact, it was the only drug that reduced diabetes-related death rates, heart attacks, and strokes. Metformin lowers fasting blood glucose levels by an average of 25% (17 to 37%), postprandial blood glucose up to 44.5%, and the A1c by an average of 1.5% (0.8 to 3.1%). Metformin reduces raised plasma insulin levels in cases of metabolic syndrome by as much as 30% and reduces the need for injected insulin in Type 2s by 15 to 32%.

Metformin is available under the trade name Glucophage, or as an extended-release tablet called Glucophage XR. It works well when combined with sulfonylureas. A combination of glyburide and metformin is also available. Combined therapy leads to a greater reduction in blood sugar than can be attained by either class alone. Generic metformin is available at a reduced cost.

Metformin possesses some distinct advantages in treating diabetes. Excess glucose produced by the liver (Gluconeogenesis) is the major source of high blood sugars in Type 2 diabetes and is typically the reason for high blood sugars on waking in the morning. Metformin reduces this overproduction of glucose. It helps in lowering the blood sugar, especially after eating, with no risk of hypoglycemia when used alone. Modest improvement in cholesterol levels is also seen.

Because metformin shuts off the liver's excess production of glucose, it reduces the amount of injected insulin needed to control the blood sugar in both Type 1 and Type 2 diabetes. People with Type 2 diabetes who are on insulin usually are advised to lower their insulin doses prior to starting metformin. The full improvement in glycemic control and cholesterol levels may not be seen until 4 to 6 weeks of use have passed.

Side effects from metformin include a change in taste, loss of appetite, nausea or vomiting, abdominal bloating or gas, diarrhea, or skin rash. These may occur during the first few weeks of taking the medication but are seldom long-lasting. Taking the medication with food and starting out with a low dose help reduce side effects. The dosage can be gradually increased as side effects diminish.

Lactic acidosis, the serious but rare side effect originally seen with phenformin, results when a build-up of lactic acid occurs due to an inability to clear metformin from the system. Lactic acidosis occurs very rarely, only once in every 30,000 person-years of use. It almost always occurs in older people who have another major health problem, especially one that may impair breathing or circulation. Warning signs of lactic acidosis include fast and shallow breathing, diarrhea, severe muscle aches, cramping, unusual weakness or tiredness, or feeling cold. Because lactic acidosis has a mortality rate of about 40%, anyone who has significant lung disease, congestive heart failure, or kidney disease should never

take this drug.

Drinking alcohol while taking metformin may also trigger lactic acidosis. It should not be used by those who use more than two ounces or two drinks of alcohol a day, who have congestive heart failure, or who have significant kidney, liver, or lung disease. Cimetidine, an H2 receptor antagonist and P450 inhibitor, may enhance the effects of metformin; therefore, the dose of metformin may need to be lower.

Although not yet FDA approved, metformin is now in clinical trials for treatment of teens who have developed Type 2 diabetes. Some pediatricians also prescribe it, on occasion, to help control a strong Dawn Phenomenon seen in a growing teen with Type 1 diabetes. This use is also not approved. It also helps lower insulin resistance in women with polycystic ovary disease. One side-effect for these women, sometimes a desired outcome, is a greater likelihood of pregnancy. [3]

Metformin Target Organ: Liver, secondary effects on muscle and fat. Action: Lower glucose production by liver, increase number of insulin receptors on muscle and fat cells Lowers HbA1c by 1.5% to 2.0% Time to reach maximum effect: 2-4 hrs Taken: with meal				
Drug	**Acts Over**	**Dose Range**	**Doses/Day**	
Glucophage (metformin)	8-12 hrs	500 - 2550 mg	2-3	

Glucophage XR (metformin)	24 hrs	500 - 2250 mg	1		
metformin + glyburide	12-18 hrs	250/1.25 to 2000/20 mg	2-3		
Side Effects: bloating, fullness, nausea, cramping, diarrhea, vit B12 deficiency, headache, metallic taste, agitation, lactic acidosis					
Contraindications: DKA(diabetic ketoacidosis), alcoholism, binge drinking, kidney or liver disease, congestive heart failure, pregnancy, use of contrast media, surgery, heart attack, age > 80					

4. THIAZOLIDINEDIONES

Thiazolidinediones or glitazones are the first class of medication designed to reverse the basic problem in Type 2 diabetes of resistance to insulin. Insulin resistance appears to be associated with high blood pressure and the high triglycerides/low HDL cholesterol problem that puts many people with Type 2 diabetes at risk for heart disease.

The drugs currently available in this group, Avandia (rosiglitazone) and Actos (pioglitazone), reverse insulin resistance by improving the sensitivity of insulin receptors in muscle, liver, and fat cells. This helps the body use insulin better.
Mechanism of action

They improve sensitivity partly by reducing levels of inflammatory cytokines like tumor necrosis factor alpha, while increasing activity of the PPAR (peroxisome proliferator-activated receptor) gamma receptor. Genes shown to be affected by PPARg action include those encoding glucokinase, GLUT4, malic enzyme, lipoprotein lipase, fatty acyl-CoA synthase and adipocyte fatty acid binding protein. Given that PPARg is predominantly expressed in adipose tissue, the effects of PPARg agonists seen in the liver and skeletal muscle may be exerted via endocrine signaling from adipocytes. Recently it was shown that mutations in the PPARg gene were correlated to familial insulin resistance.

They also help keep the liver from overproducing glucose. They have been shown to lower blood sugar levels about 15% while at the same time lowering insulin levels by 20%. In Type 2, insulin levels are raised as the body produces more insulin than normal to try to overcome insulin resistance. Lower insulin levels indicate that these drugs are decreasing insulin resistance.

In addition to improving insulin sensitivity, glitazones may decrease cardiac risks. They raise the LDL level slightly, but increase the size of the LDL molecule. This may make LDL less harmful, because small, dense LDL is the type most likely to clog blood vessels. Glitazones also lower alpha tumor necrosis factor, an inflammatory particle that is associated with an increased risk of heart disease. Blood pressure and triglyceride levels are somewhat reduced, while HDL levels are slightly raised. Newer glitazones, which work on other PPAR receptors and are currently in clinical trials, also seem to lower high triglycerides and raise the low levels of protective HDL cholesterol commonly seen with insulin resistance.

Glitazones decrease insulin resistance and improve cholesterol, lipid and glucose

levels around the clock. Their greatest effect on the blood glucose occurs after eating. They do not cause hypoglycemia when used alone, but can cause lows if used with a sulfonylurea or insulin.

Less insulin is required to control blood sugars when glitazones are used. This means that doses of other drugs that increase insulin production, like sulfonylureas or insulin itself may need to be reduced when a glitazone is started.

Avandia and Actos may produce side effects, such as water retention and swelling of the ankles, especially in older people. Other possible side effects include weight gain, muscle weakness, and fatigue. Because they lower insulin resistance, they also increase fertility in younger women who have polycystic ovary disease, called PCOS. If pregnancy is not desired, a premenopausal woman using one of these drugs should be careful to use birth control. Although they have been shown to rarely cause liver damage, the FDA requires that liver tests be done before treatment start, every two months for the first year and periodically thereafter. If the liver enzyme ALT shows a value more than three times the upper limit of normal, the drug must be stopped.

The glitazones work well in Type 2 diabetes only when insulin resistance is present. People with Type 1.5 diabetes, caused by a lower production of insulin rather than resistance to insulin, are unlikely to benefit from a glitazone. The presence of excess abdominal weight, a low HDL level, high triglycerides, or high blood pressure, all associated with insulin resistance, are good indicators that glitazones may be worth trying.

Glitazones
Target Organ: muscle, fat, and liver

Action: improve receptivity of insulin receptors, reduce glucose production by liver
Lowers HbA1c by 0.5% to 1.5%

Time to reach maximum effect: 6 - 8 weeks

Taken: with or without food

Drug	**Dose Range**	**Doses/Day**
Actos (pioglitazone)	15 - 45 mg	1
Avandia (rosiglitazone)	2 - 8 mg	1 - 2

Side Effects: swelling of legs, fluid retention, weights gain(upper respiratory tract infections, headaches, muscle aches, tooth aches, sore throat in less than 1%)

Contraindications: kidney or liver disease, enlarged heart, congestive heart failure, edema, pregnancy

5. A-GLUCOSIDASE INHIBITORS

Alpha-glucosidase inhibitors or starch blockers such as acarbose and miglitol function by interfering with the action of the a-glucosidases present in the small intestinal brush border. The consequence of this inhibition is a reduction in digestion and the consequent absorption of glucose into the systemic circulation. The reduction in glucose uptake allows the pancreatic b-cells to more effectively regulate insulin secretion; they are taken with every meal. The advantage to the use of the a-glucosidase inhibitors is that they function locally in the intestine and have no major systemic action. Hypoglycemia does not usually occur with the use of a-glucosidase inhibitors but they are effective at reducing fasting plasma glucose (FPG) levels and levels of glycosylated hemoglobin (HbA_{1c}). The common adverse side effects of these inhibitors are abdominal bloating and discomfort, diarrhea and flatulence.

The way in which starch blockers work is also the source of their side effects. Although they are very safe because they usually enter the bloodstream in negligible amounts, their side effects within the intestine can be annoying. If digestion is greatly inhibited, abdominal bloating, gas, and diarrhea can result. A very good way to minimize or prevent intestinal side effects is to start these medications at minimal doses and then gradually increase them as tolerance improves in a week or so. Half of the smallest tablet can be started before one meal a day, then gradually the dose can be increased and extended to all meals this way. Side effects tend to decrease over time, allowing doses to be increased. Anyone who has problems with digestion or absorption will need to take extra care with these medications.

If acarbose and miglitol are taken with insulin or another diabetes medication that can cause low blood sugars, the lows are best treated with glucose tablets or a glucose gel. Digestion of sugar, fruit, and fruit juice is delayed by starch blockers, so they will not raise a low blood sugar as quickly.

Like metformin, these drugs do not cause low blood sugars when used alone, nor do they cause weight gain or raise insulin levels. Because they work in a unique way, they can be added to other oral agents to improve blood sugar results. [5]

Starch Blockers

Target Organ: Intestine

Action: Slow breakdown of carbs in intestine
Lowers HbA1c by 0.7% to 1.0%

Time to reach maximum effect: 1 hrs

Taken: before meals with first bite of food

Drug	Acts Over	Dose Range	Doses/Day
Precose (acarbose)	4 hrs	25 - 300 mg	3
Glyset (miglitol)	4 hrs	25 - 300 mg	3

Side Effects: bloating, nausea, diarrhea, excess gas, abdominal pain

Contraindications: liver disease, bowel or intestinal disease, intestinal obstruction

The Incretins: GLP-1 Agonists and DPP-4 Inhibitors

In 1902, Researchers first hypothesized that the gut might directly signal the pancreas. Later in 1930, the term incretin was first used to describe the enhanced glucose lowering effect that was seen when a gut extract was fed to dogs. In the 1960s, researchers discovered that almost twice as much insulin was released when they infused glucose directly into the gut rather than into the blood as an IV solution. This discovery of an increase in insulin release renewed interest in a search for compounds produced by the gut that could lower blood glucose levels.

The first incretin to receive FDA approval in May of 2005 was Byetta. Byetta is a **GLP-1 (glucagon-like peptide-1)** like drug or agonist and is rather unusual in that it is derived from a compound found in the saliva of the Gila monster, a large lizard native to the southwestern US. It is currently available as a prescription for people with Type 2 diabetes who are not on insulin.

GLP-1 or glucagon-like peptide 1 is one of several incretin compounds that have biologic activity. After release into the blood by the intestine in response to food intake, GLP-1 slows food absorption. This delay in absorption allows the slow insulin response found in Type 2 diabetes to catch up. Improved insulin production also occurs when people take GLP-1 agonists. Both an increase in beta cell mass and improvement of first phase insulin release toward normal have been seen with this drug. Researchers hope that this action may delay progression of Type 2 diabetes or possibly assist in recovery of beta cell activity in early Type 1 diabetes. GLP-1 agonists have multiple sites of action.

So far, the reduction of glucose levels, blood pressure, and weight plus an increase in well being all appear positive. Side effects like nausea that does not go away on minimal doses may require that the medication be stopped or that smaller starting doses be given with a syringe rather than using the standard starting dose of 5 mg that is provided in the Byetta pen.

In addition to the delay in food absorption, GLP-1 agonist also stimulate insulin production and restore first phase insulin secretion. The overall effect is to decrease the postmeal blood sugars and improve control without the risk of hypoglycemia. Research has shown that people on Byetta eat about 20% less and often lose weight.

Giving natural GLP-1 was found to have little benefit because it is broken down by an enzyme called DPP-4 (dipeptidyl peptidase IV) within about 5 minutes. This lead to a search for modified GLP-1 molecules like Byetta, produced, that are not broken down as quickly. Other new GLP-1 derivatives are currently in clinical trials ex. liraglutide

Related to the GLP-1 agonists is a second new class of diabetes medications called **DPP-4 Inhibitors** which work by delaying the breakdown of GLP-1, as well as other incretins. Because DPP-4 is involved in the break down of several peptides in the body, it will take time to be sure there are no unwanted long-term side effects. The major clinical advantages to the use of DPP IV inhibitors are that the ones in current trials are orally delivered. Compliance in patients is much higher with orally delivered drugs than with those that require injection. **Sitagliptin** has recently been approved for use alone or in combination with either metformin or the thiazolidinediones.

Conclusion

As we have already mentioned diabetes is a disease that affects millions of people all over the world from all ethnic, social, age and economic groups. It has devastating effects and causes thousands of deaths from coronary heart disease, renal failure, strokes or even plain straightforward hypoglycaemia. It also degrades the quality of life of its victims by affecting their vision, making them more prone to infections or even by leading to amputation of body limbs due to peripheral vascular disease.

The medications we currently use have enabled us to significantly improve the progress and outcome of diabetes for most of the patients. But there are still many drawbacks. Until now we were not able to mimic the function of the human pancreas. There are limitations in the ways an average patient has to continuously monitor his blood sugar and efficiently administer treatment.

Most currently available techniques are more or less invasive and the administration of the medication sometimes could be a painful or mentally stressful procedure not well tolerated by the patients. Even in the best cases there is no continuous and analogous response to the constantly changing glucose levels in the blood thus leading to spikes of hyperglycaemia during the day or occasionaly to hypoglycaemic episodes of variable gravity.

The complexity of the medication metabolism in the human body and the unique response of every individual patient to treatment creates great challenges for pharmacists and doctors. We can slow down the disease but ultimately in time it still wins.

Modern medicine promises future treatment or even cure of the disease by exotic ways like stem cell therapy or transplant cultures in animals or even xeno-transplantations. But all these methods have a long way to go before they are implemented in clinical practice.

Modern pharmacy on the other hand in close contact with medicine has presented some latest procedures which might be appliable very soon and might help us to combat diabetes even more effectively now.

Insulin pumps that will enable constant blood sugar monitoring and appropriate insulin release are within our current abilities. Insulin administration via inhalers is going to improve patient compliance and give better results in combating the disease and this is a reality now.

Research in the molecular level for newer medication with fewer side effects is getting good results and more answers are coming in every day about the way diabetes works.

The pharmaceutical community in coordination with doctors, biochemists, genetics specialists and countless others wins smaller or larger battles against diabetes everyday and although the end of the war lies far in the future our achievements so far allow us to hope. And hope is the first big step to success.

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