A Review on Diabetes Mellitus

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Abstract
Diabetes is a chronic disease that occurs when the pancreas does not generate enough insulin, or when the body cannot effectively use the insulin it produces. Hyperglycaemia, or raised blood sugar, is a common effect of uncontrolled diabetes and over time leads to severe damage to many of the body's systems, especially the nerves and blood vessels. DM can also occur secondary to genetic defects in beta cell function or insulin action, pancreatic diseases or other endocrinopathies, medications, toxic chemicals, or uncommon forms of immune-mediated diabetes, e.g., "stiff man syndrome" or the presence of anti-insulin receptor antibodies.

Key words: Diabetes, stiff man syndrome, Hyperglycaemia.

INTRODUCTION
Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects of insulin secretion and/or increased cellular resistance to insulin. Chronic hyperglycemia and other metabolic disturbances of DM lead to long-term tissue and organ damage as well as dysfunction involving the eyes, kidneys, and nervous and vascular systems [1-3]. The definitions and categories of DM used in this document are based on the most recent classifications reported by the American Diabetes Association [4-5].

CLASSIFICATION
The Classification Of DM Has Undergone The Following Important Changes
1. The designations “type 1 diabetes” and “type 2 diabetes,” using Arabic numerals, replace the terms “insulin dependent diabetes mellitus” (IDDM) and “non-insulin dependent diabetes mellitus” (NIDDM).
2. A new term, “IFG” (impaired fasting glucose), defines glucose values that are greater than or equal to 100 mg/dl and up to 125 mg/dl.
3. The revised diagnostic criteria for DM are:
   A. A1C level \( \geq 6.5\% \). Diagnosis should be confirmed with repeat A1C test unless clinical symptoms and glucose levels \( \geq 200 \text{ mg/dl} \) are present. (Prior criteria should be used in the absence of A1C testing.) 6
   B. Symptoms of hyperglycemia plus casual plasma glucose concentration greater than or equal to 200 mg/dl. "Casual" is defined as any time of the day without regard to time since the last meal. Classic symptoms of hyperglycemia include polyuria, polydipsia, and unexplained weight loss.
   or
   C. Fasting plasma glucose greater than or equal to 126 mg/dl. "Fasting" means no caloric intake for at least 8 hours. A test yielding an abnormal result must be repeated on a different day.
   or
   D. Two-hour plasma glucose greater than or equal to 200 mg/dl during an oral glucose tolerance test (OGTT), using a 75-g glucose challenge, as described by the World Health Organization (WHO) [5].

A. Type 1 diabetes mellitus
The American Diabetes Association provides clear definitions of the various types of diabetes and classification, diagnosis, and clinical care of diabetes. Type 1 DM, which results from destruction of beta cells in the pancreas, accounts for approximately 10 percent of all patients with DM in the United States. It leads to absolute insulin deficiency. There are two forms of type 1 DM. One is an immune-mediated disease with autoimmune...
B. Type 2 diabetes mellitus
Type 2 is the most common form of DM worldwide, and its prevalence is increasing. Its underlying defects can vary from predominant insulin resistance with relative insulin deficiency to a predominant insulin secretory defect with insulin resistance. A great deal of heterogeneity exists, and most patients with type 2 DM do not initially require insulin therapy. Accounting for approximately 90 percent of all cases of DM in the United States, type 2 DM occurs more frequently in adults than in children, and the incidence increases with age, especially after age 40. However, the prevalence of type 2 DM in children is increasing, especially in the high-risk ethnic groups, such as Native Americans, Hispanic Americans, African Americans, and Asian Americans. Most of these children are between 10 and 19 years old, have had symptoms longer, have infrequent or mild diabetic ketoacidosis, are obese, and have a strong family history of diabetes. A characteristic finding is darkening of the skin (acanthosis nigricans) and there is an increased incidence of insulin resistance [7-8]. Because the onset is frequently insidious, many patients with type 2 DM are asymptomatic and remain undiagnosed for years. Upper body obesity is a recognized risk factor because it results in peripheral insulin resistance. The beta cells compensate for this resistance by increasing insulin secretion and maintaining normal glucose tolerance. Eventually, the hyperglycemia worsens, glucose toxicity ensues, and insulin secretion and action decrease. Ultimately, the loss of beta cell mass can lead to insulin dependency. The expanded definition of the insulin resistance syndrome now includes glucose intolerance, hypertension, dyslipidemia (high triglycerides, low HDL cholesterol, and increased LDL), increased plasminogen activator inhibitor (PAI-1) levels, reduced sex-binding globulin, coronary artery disease, and diffuse atherosclerosis. These findings may be the basis for the marked increase in coronary heart disease reported in type 2 DM.

C. Impaired fasting glucose and impaired glucose tolerance
Patients with hyperglycemia at levels that are below the diagnostic criteria for DM are diagnosed with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), depending on the test used: IFG, by the fasting plasma glucose (FPG) test; IGT, by the oral glucose tolerance test (OGTT). In IFG, the fasting glucose levels are greater than or equal to 100 mg/dl and up to 125 mg/dl; for IGT, the 2-hour plasma glucose value is greater than or equal to 140 mg/dl and up to 199 mg/dl. Most individuals with IFG and IGT are euglycemic in daily life and often have normal glycosylated hemoglobin (HbA1C) levels. Both IFG and IGT are risk factors for future DM. Serial testing shows that such patients may improve, remain stable, or worsen. Neither IFG nor IGT is associated with the microvascular complications of DM, but they have been linked with macrovascular disease.

D. Gestational diabetes mellitus
By definition, gestational diabetes mellitus (GDM) is any degree of glucose intolerance with onset or first diagnosis during pregnancy. Usually diagnosed during the second or third trimester, GDM occurs in approximately 4 percent of pregnancies or 135,000 cases annually. The prevalence rate of 1–14 percent depends upon the population studied. Glucose tolerance usually returns to normal within 6 weeks after pregnancy ends, at which time the woman needs to be reclassified. Most GDM patients do not develop DM later in life, but some will
develop IFG, IGT, type 2 DM, or even type 1 DM. Because increased fetal mortality and morbidity have been associated with GDM, prompt detection and aggressive treatment are important. GDM remains a subgroup within the new classification, but the screening criteria have been revised. No longer do all pregnant women require screening; those exempted must meet all of the following criteria:
1. Less than 25 years of age
2. Normal weight before pregnancy
3. Member of an ethnic group with low prevalence of DM
4. No known DM in first-degree relatives
5. No history of abnormal glucose tolerance and
6. No history of poor obstetric outcome
Risk assessment should be conducted early in the pregnancy and glucose testing should be conducted promptly for those with risk characteristics. For women with risk characteristics whose initial screening shows no sign of GDM, follow-up screening should be performed between 24 and 28 weeks, using an OGTT [9].

E. Other Specific Types of Diabetes
DM can also occur secondary to genetic defects in beta cell function or insulin action, pancreatic diseases or other endocrinopathies, medications, toxic chemicals, or uncommon forms of immune-mediated diabetes, e.g., “stiff man syndrome” or the presence of anti-insulin receptor antibodies. The defects in beta cell function are better characterized since linkage of chromosome 7 to the glucokinase deficiency found in maturity-onset diabetes of the young (MODY) 2. MODY 3 is linked to chromosome 12 and MODY 1 to chromosome 20.49 Although few patients have DM related to these other entities, the clinician interpreting blood glucose screening results must consider the patient’s medical history.

THE HISTORY OF DIABETES
The historical aspects of diabetes are:
• 1552 BCE
Egyptian physician Hesy-Ra of the 3rd Dynasty makes the first known mention of diabetes – found on the Ebers Papyrus and lists remedies to combat the ‘passing of too much urine.’
• 250 BCE
Diabetes described by Arateus as ‘the melting down of flesh and limbs into urine.’
• 120 BCE
Greek physician Aretaeus of Cappodocia gives the first complete medical description of diabetes, which he likens to ‘the melting down of flesh and limbs into urine.’
• 1425
Diabetes first appears in the English language as the Middle English word ‘diabe’t.’
• 16th Century
Swiss physician Phillipus Aureolus Paracelsus – considered the ‘Martin Luther of Medicine’ – identifies diabetes as a serious general disorder.
• 1674
In his treatise Pharmacoeuticæ rationalis, Professor Thomas Willis of Oxford University describes the ‘wonderfully sweet’ flavour of urine in diabetes mellitus.
• 1776
English physician Matthew Dobson of Liverpool evaporates two quarts of urine from a patient with diabetes. The resulting residue is granulated and smells and tastes like sugar, conclusively establishing the presence of ‘saccharine materials’ as a diagnosis of diabetes.
• 1797
Scottish physician John Rollo creates the first medical therapy to treat diabetes. He prescribes an ‘animal diet’ for his patients of ‘plain blood puddings’ and ‘fat and rancid meat’ so to manage the disease with foods their bodies could assimilate.
• 1869
German medical student Paul Langerhans discovers the islet cells of the pancreas but is unable to explain their function. The find is dubbed the ‘islets of Langerhans.’
• 1871
French physician Apollinaire Bouchardat notices the disappearance of glycosuria in his diabetes patients during food rationing of food under the Siege of Paris in the Franco-Prussian War, and formulates individualized diets to treat the condition.
• 1889
Scientists Oskar Minkowski and Joseph von Mering of the University of Strasbourg, France demonstrate how removing a dog’s pancreas produces diabetes.
• 1901
American pathologist Eugene Opie of John Hopkins University in Baltimore establishes a connection between the failure of the islets of Langerhans in the pancreas and the occurrence of diabetes.
Prof. John J.R. Macleod writes a monograph on diabetes entitled ‘Diabetes: Its Pathological Physiology.’

**Dec. 1916**
Boston pathologist Elliott Joslin compiles 1,000 of his own cases and creates the textbook The Treatment of Diabetes Mellitus. In it he reports that ‘the mortality of patients was approximately 20 per cent lower than for the previous year’, due to ‘the introduction of fasting and the emphasis on regular exercise.’ This book and Joslin’s subsequent research over the next five decades establishes his reputation as one of the world’s leading expert in diabetes.

**1919**
Dr. Frederick Allen of the Rockefeller Institute in New York publishes his Total Dietary Regulations in the Treatment of Diabetes that introduces a therapy of strict dieting – dubbed the ‘starvation treatment’ as a way to manage diabetes.

**Oct. 31, 1920**
Banting conceives of the idea of insulin after reading an article in the journal Surgery, Gynecology and Obstetrics by Moses Barron, an American pathologist, titled ‘The Relation of Islets of Langerhans to Diabetes with Special Reference to Cases of Pancreatic Lithiasis.’ He moves to Toronto and over the next year, with the support of Prof. Macleod of the University of Toronto, and the assistance of Best, a medical student, and Dr. James Collip, continues his research using a variety of different extracts on depancreatized dogs.

**Summer 1921**
Banting’s work leads to the discovery of insulin. On July 30, Dog 410 is the first to receive the extract. On August 4 the extract is called ‘Isletin’ for the first time.

**Nov. 14, 1921**
Dr. Banting and Charles Best deliver a preliminary report of their research to the Journal Club of the University of Toronto, Department of Physiology.

**Nov. 17, 1921**
Banting and Best discover that extract from cattle foetal pancreas lowers blood sugar levels of depancreatized dogs, leading them toward plentiful, cheap sources for insulin. Experiments begin to test the long-term effectiveness of insulin treatment.

**December 1921**
Dr. James Bertram Collip, a biochemist on sabbatical from the University of Alberta, joins the Banting and Best team to assist in refining the quality of extracts.

**Dec. 30, 1921**
Banting, Macleod, Best and Collip present the results of their research at a session of the American Physiological Society at Yale University. The paper initially generates little interest. The paper – ‘The Internal Secretion of the Pancreas’ – is published two months later in the prestigious Journal of Laboratory and Clinical Medicine.

**January 1922**
Leonard Thompson, 14, a ‘charity patient’ at the Toronto General Hospital, becomes the first person to receive and injection of insulin to treat diabetes. Thompson lives another 13 years before dying of pneumonia at age 27.

**May 3, 1922**
The word ‘insulin’ is used in public for the first time when Macleod presents the paper ‘The Effect Produced on Diabetes by the Extracts of Pancreas’ to the Association of American Physicians annual meeting in Washington, D.C. The results of the Toronto group’s experiments is hailed as ‘one of the greatest achievements of modern medicine’.

**May 30, 1922**
Pharmaceutical manufacturer Eli Lilly & Co. of Indianapolis and the University of Toronto enter a deal for the mass production of insulin.

**Aug. 16, 1922**
Elizabeth Evans Hughes, 13, daughter of U.S. Secretary of State Charles Evans Hughes, arrives in Toronto to be treated by Banting for her diabetes. Weighing only 45 pounds and barely able to walk, Elizabeth responds immediately to the insulin treatment, and goes on to live a productive life. She dies in 1981 at age 73.

**Oct. 25, 1923**
Banting and Macleod are awarded the Nobel Prize in Physiology or Medicine. Banting shares his award with Best, while Macleod shares his with Collip.

**October 1923**
Insulin is made commercially available in the United States and Canada.

**1936**
In a series of research papers, Sir Harold Himsworth of the University College Hospital in London finds that diabetes falls into two types based on ‘insulin insensitivity.’ This discovery later leads to the diabetes classifications of type 1 and type 2.

**1936**
Hans Christian Hagedorn, founder of Novo Nordisk, discovers that adding protamine to insulin prolongs the duration of action of the medication.

**Feb. 21, 1941**
At the height of the Second World War, Major Banting is killed in an airplane crash over Newfoundland while on a secret mission to England.

- 1944
  The standard insulin syringe is introduced so to make diabetes management more uniform.

- 1949
  Best co-founds the Diabetic Association of Ontario.

- 1953
  Canadian Diabetes Association is established and Camp Banting, Canada’s first camp for children with diabetes, opens near Ottawa.

- 1959
  Researchers identify type 1 diabetes (insulin dependent) and type 2 diabetes (non-insulin dependent).

- 1966
  First pancreas transplant performed at the University of Manitoba

  - Sept. 14, 1971
    Anton Hubert Clemens receives the first patent for a portable blood glucose meter called the Ames Reflectance Meter. Dr. Richard K. Bernstein, an insulin dependent physician with diabetes, uses the meter to monitor his blood glucose at home, and subsequently publishes a report on his experiences.

- 1970
  A group of interested physicians form the Clinical and Scientific Section (C&SS) of the Canadian Diabetes Association

- 1972
  The Canadian Diabetes Association establishes the Diabetes Educators Section (DES) to represent nurses, dietitians, physicians, social workers and other healthcare professionals.

- 1978
  David Goeddel from pharmaceutical firm Genentech indicated that the first rDNA human insulin was created. Later that year, Genentech and pharmaceutical firm Eli Lilly signed an agreement to commercialize biosynthetic human insulin.

- 1982
  The first biosynthetic human insulin – Humulin – that is identical in chemical structure to human insulin and can be mass produced was approved to market in several countries.

- 1989
  Her Majesty Queen Elizabeth The Queen Mother kindles the Flame of Hope at Banting House National Historic Site – ‘The Birthplace of Insulin’ – in London, Ontario. As a symbol of hope, the flame will burn until a cure for diabetes is found.

  - November 5, 1991
    As part of the 100th anniversary of Dr. Banting’s birth, a time capsule created by the International Diabetes Federation Youth Representatives is entombed by Governor General Ray Hnatyshyn at Banting House in London, Ontario. The capsule will be opened when a cure for diabetes is found.

- 1992

- 1993
  After 10 years of clinical study, the Diabetes Control and Complications Trial (DCCT) report is published and clearly demonstrates that intensive therapy delays the onset and progression of long-term complications in individuals with type 1 diabetes.

- 1995
  Canadian Diabetes Association launches its website which quickly becomes a source of diabetes-related information for people all over the world.

- 1996
  75th Anniversary of the discovery of insulin is celebrated around the world.

- 1998
  The United Kingdom Prospective Diabetes Study (UKPDS) scientifically inks the control of glucose levels and blood pressure control to the delay and possible prevention of type 2 diabetes.

- 1998
  The Clinical Practice Guidelines for the Management of Diabetes in Canada is released by the Canadian Diabetes Association, and become a model for other nations health programs.

- March 1999
  Scientists conduct the first successful islet transplant at the University of Alberta Hospital. The surgical procedure becomes known as The Edmonton Protocol.

- July 7, 1999
  Banting House is officially declared a National Historic Site. In a designation ceremony at Dr. Banting’s historic home, Governor General Romeo LeBlanc unveils the Historic Sites and Monuments Board of Canada plaque.

- Dec. 15, 2003
  Canadian Diabetes Association posts the 2003 Clinical Practice Guidelines on its website as the first searchable, download-capable medical guidelines available online.
• Dec. 20, 2006
The United Nations recognizes diabetes as a global threat and designates World Diabetes Day, November 14 – in honour of Frederick Banting’s birthday – as a UN Day to be observed every year starting in 2007.
• Dec. 17, 2008
This article was originally published in Diabetes Health in November, 1996.
• For 2,000 years diabetes has been recognized as a devastating and deadly disease. In the first century A.D. a Greek, Aretaeus, described the destructive nature of the affliction which he named “diabetes” from the Greek word for “siphon.” Eugene J. Leopold in his text Aretaeus the Cappodacian describes Aretaeus’ diagnosis: “...For fluids do not remain in the body, but use the body only as a channel through which they may flow out. Life lasts only for a time, but not very long. For they urinate with pain and painful is the emaciation. For no essential part of the drink is absorbed by the body while great masses of the flesh are liquefied into urine”.
• Physicians in ancient times, like Aretaeus, recognized the symptoms of diabetes but were powerless to effectively treat it. Aretaeus recommended oil of roses, dates, raw quinces, and gruel. And as late as the 17th century, doctors prescribed “gelly of viper’s flesh, broken red coral, sweet almonds, and fresh flowers of blind nettles”.
• Early Discoveries-Human Guinea Pigs
• In the 17th century a London physician, Dr. Thomas Willis, determined whether his patients had diabetes or not by sampling their urine. If it had a sweet taste he would diagnose them with diabetes mellitus- “honeyed” diabetes. This method of monitoring blood sugars went largely unchanged until the 20th century.
• Despite physicians’ valiant efforts to combat diabetes, their patients remained little more than human guinea pigs. In the early 20th century, diabetologists such as Dr. Frederick Allen prescribed low calorie diets-as little as 450 calories per day for his patients. His diet prolonged the life of people with diabetes but kept them weak and suffering from near starvation. In effect, the most a person afflicted with diabetes could do was blindly offer himself to the medical establishment and pray for a cure. In his book, The Discovery of Insulin, Michael Bliss describes the painful wasting death of many people with diabetes before insulin: “Food and drink no longer mattered, often could not be taken. A restless drowsiness shaded into semi-consciousness. As the lungs heaved desperately to expel carbonic acid (as carbon dioxide), the dying diabetic took huge gasps of air to try to increase his capacity. ‘Air hunger’ the doctors called it, and the whole process was sometimes described as ‘internal suffocation.’ The gasping and sighing and sweet smell lingered on as the unconsciousness became a deep diabetic coma.
• The Miraculous Discovery-Insulin
• Then in 1921 something truly miraculous occurred in Ontario, Canada. A young surgeon Frederick Banting, and his assistant Charles Best, kept a severely diabetic dog alive for 70 days by injecting it with a murky concoction of canine pancreas extract. With the help of Dr. Collip and Dr. Macleod, Banting and Best administered a more refined extract of insulin to Leonard Thompson, a young boy dying of diabetes. Within 24 hours, Leonard’s dangerously high blood sugars had dropped to near normal levels. Until the discovery of insulin, most children diagnosed with diabetes were expected to live less than a year. In a matter of 24 hours the boy’s life had been saved. News of the miracle extract, insulin, spread like wildfire across the world.
• In 1935 Roger Hinsworth discovered there were two types of diabetes: “insulin sensitive” (type I) and “insulin insensitive” (type II). By differentiating between the two types of diabetes, Hinsworth helped open up new avenues of treatment.
• Starting in the late 1930s, new types of pork and beef insulin were created to better manage diabetes. PZI, a longer acting insulin, was created in 1936. In 1938 NPH insulin was marketed, and in 1952 Lente, containing high levels of zinc which promotes a longer duration of action was invented.
• In the 1950s, oral medications-sulfonylureas were developed for people with type II. These drugs stimulate the pancreas to produce more insulin, helping people with type II diabetes keep tighter control over their blood sugars.
• In the 1960s urine strips were developed. Dorothy Frank, who has had type I diabetes since 1929, remembers, “In order to test your blood sugars there were these do-it-yourself urine kits-blue meant there was no sugar present, and orange meant you were positive.” With the invention of urine strips, it was no longer necessary to play chemist, with a collection of test tubes lined up on the bathroom sink, waiting for the results.
Becton-Dickinson introduced the single use syringe in 1961. This greatly reduced the amount of pain from injections as well as the time-consuming ritual of boiling needles and glass syringes. Diabetes Health board member Dr. Nancy Bohannon describes the early syringes: “The needles were enormous, and they came with little pumice stones so that you could sharpen them. They often became dull and developed barbs on the end. And in order to sterilize them they had to be boiled for twenty minutes.”

The first portable glucose meter was created in 1969 by Ames Diagnostics. Diabetes Health board member Dr. Richard Bernstein, in his book titled Diabetes Type II, Including Type I, describes his first Ames meter: “In October of 1969, I came across an advertisement for a new device to help emergency rooms distinguish between unconscious diabetics and unconscious drunks when the laboratories were closed at night. The instrument had a four-inch galvanometer with a jeweled bearing, weighed three pounds, and cost $650.” Dr. Bernstein describes one particularly bizarre incident he experienced while carrying his Ames Eyetone Meter. “One day I arrived early at our attorney’s office for a meeting of the board of directors. I was carrying my meter in a bag, and I hung it up in the coat room. A few minutes later everyone was in a panic, saying a bomb had been found in the coat room. The entire 24 story building was being evacuated. It took me some time to convince the bomb squad not to blow up my meter.”

Since then, new technologies have brought us glucose meters the size of calculators that can be easily carried in a pocket or purse. Thankfully, the days of hefting around a three pound glucose meter are over.

In the late ‘70s the insulin pump was designed to mimic the body’s normal release of insulin. The pump dispenses a continuous insulin dosage through a cannula (plastic tube), using a small needle that is inserted into the skin. The first pumps, created in 1979, were large and bulky and had to be carried in a backpack. Linda Fredrickson, RN, director of the Professional Education and Clinical Services at MiniMed, describes her first insulin pump: “My first pump in 1980 was an Auto-Syringe, which weighed 17 ounces and had blinking red lights. People nicknamed them the ‘blue brick.’”

Fortunately, technology has allowed for great leaps in pump design. The pumps of today are light and compact and can easily be carried in a pocket or clipped to a belt.

In 1979 Derata released the first needle-free insulin delivery system—the Derma-Ject. It weighed 1-1/2 pounds and cost $925 dollars. The Derma-Ject carried the insulin on the side and had no pressure adjustment feature. One early user of the Derma-Ject decided not to use it after a month because it gave him such a terrible jolt every time he used it. Thankfully, modern needle-free injectors have adjustable pressure, so they are relatively pain free. In addition, the newer models are light and compact in comparison to the heavier models of the ‘70s.

The hemoglobin A1c test was devised in 1979 in order to create a more precise blood sugar measurement. With the A1c, hemoglobin, the oxygen-carrying pigment in red blood cells, is used to track glucose changes over a period of four months, the life span of the cell. Hemoglobin links with the glucose in blood; the more glucose present, the greater amount of hemoglobin linked with glucose. The A1c became a standard measurement for blood sugar control in the comprehensive ten-year study from 1983 to 1993—the Diabetes Control and Complications Trial (DCCT).

With the conclusion of the DCCT in 1993, studies showed that people who were able to keep their blood glucose levels as close to normal as possible had less chance of developing complications, such as eye, kidney and nerve disease. Before this, many doctors had not put much emphasis on tight control of blood glucose levels. The common belief for decades was that diligent monitoring of blood sugars and intensive insulin therapy had little consequence for people with diabetes. Since the DCCT’s findings, statistics have proven that tight blood glucose control can be extremely beneficial for people with diabetes.

In May of 1995, Metformin, an oral medication for people with type II diabetes, was finally approved for use in the United States by the FDA. Unlike sulfonylurea drugs, which stimulate insulin release, Metformin does not increase insulin production. Instead, it heightens sensitivity to insulin and increases the muscles’ ability to use the insulin. Since Metformin promotes weight loss, decreases hyperglycemia, and improves lipid levels, it has been shown to be an effective tool for people with type II diabetes when used in conjunction with sulfonylureas.
Precose, an oral medication, was approved for use by people with type II diabetes in September 1995. Precose delays the digestion of carbohydrates, thereby reducing the sudden rise in blood glucose after eating a meal. Precose can be used in conjunction with diet to lower blood sugars in people with type II whose glucose levels cannot be regulated through diet alone.

Lispro, a new fast-acting insulin, was released in August of 1996 by Eli Lilly under the brand name Humalog. Lispro is designed to simulate the body’s natural insulin output. Because of lispro’s fast-acting tendencies, patients can take this insulin 15 minutes or less before eating a meal, instead of waiting as they would with Regular insulin.

**The Future of Diabetes**

- Three thousand years have passed since Aretaeus spoke of diabetes as “the mysterious sickness.” It has been a long and arduous process of discovery, as generations of physicians and scientists have added their collective knowledge to finding a cure. It was from this wealth of knowledge that the discovery of insulin emerged in a small laboratory in Canada. Since insulin saved the life of young Leonard Thompson 75 years ago, medical innovations have continued to make life easier for people with diabetes.
- As the 21st century rapidly approaches, diabetes researchers continue to pave the road toward a cure. Today, it is unclear what shape the road will take; perhaps another dramatic discovery like insulin waits around the corner, or possibly researchers will have to be content with the slow grind of progress.

**SIGNS AND SYMPTOMS**

**Symptoms Of Type 1 Diabetes**

1. Frequent urination
2. Unusual thirst
3. Extreme hunger
4. Unusual weight loss
5. Extreme fatigue and Irritability

There is a reason why diabetes is termed the silent killer. It is important to bear in mind that these symptoms may be mistaken for an ailment in themselves or for some other disease. The best method to diagnose this condition is to have a blood test taken. And if you have already noticed this symptom, you should see a doctor at the earliest.

**Symptoms of Type 2 Diabetes**

1. Excessive Urination and Thirst
2. Increased Hunger
3. Unexplained Weight Gain
4. Irritability and Fatigue
5. Blurred Vision
6. Warning Signs of Diabetes
   a) Decelerated Healing
   b) Skin and Yeast Infections plus Frequent Gum and Bladder Infections

**Other Symptoms**

1. Sexual Dysfunction in Men
2. Vaginal Infections in Women
3. Numbness/Tingling in hands and feet
4. Itchy or Flaky Skin

**CAUSES**

**Cause of type 1 diabetes**

Type 1 diabetes is caused by a lack of insulin due to the destruction of insulin-producing beta cells in the pancreas. In type 1 diabetes an autoimmune disease the body’s immune system attacks and destroys the beta cells. Normally, the immune system protects the body from infection by identifying and destroying bacteria, viruses, and other potentially harmful foreign substances. But in autoimmune diseases, the immune system attacks the body’s own cells. In type 1 diabetes, beta cell destruction may take place over several years, but symptoms of the disease usually develop over a short period of time.

Type 1 diabetes typically occurs in children and young adults, though it can appear at any age. In the past, type 1 diabetes was called juvenile diabetes or insulin-dependent diabetes mellitus.

Latent autoimmune diabetes in adults (LADA) may be a slowly developing kind of type 1 diabetes. Diagnosis usually occurs after age 30. In LADA, as in type 1 diabetes, the body’s immune system destroys the beta cells. At the time of diagnosis, people with LADA may still produce their own insulin, but eventually most will need insulin shots or an insulin pump to control blood glucose levels [11-12].

**Genetic Susceptibility**

Heredity plays an important part in determining who is likely to develop type 1 diabetes. Genes are passed down from biological parent to child. Certain gene variants that carry instructions for making proteins called human leukocyte antigens...
(HLAS) on white blood cells are linked to the risk of developing type 1 diabetes [13-14].

**Autoimmune Destruction of Beta Cells**
In type 1 diabetes, white blood cells called t cells attack and destroy beta cells.

**Environmental Factors**
Environmental factors, such as foods, viruses, and toxins, may play a role in the development of type 1 diabetes, but the exact nature of their role has not been determined. Some theories suggest that environmental factors trigger the autoimmune destruction of beta cells in people with a genetic susceptibility to diabetes.

**Viruses and Infections**
A virus cannot cause diabetes on its own, but people are sometimes diagnosed with type 1 diabetes during or after a viral infection, suggesting a link between the two. Viruses possibly associated with type 1 diabetes include coxsackievirus b, cytomegalovirus, adenovirus, rubella, and mumps.

**Infant Feeding Practices**
Some studies have suggested that dietary factors may raise or lower the risk of developing type 1 diabetes. For example, breastfed infants and infants receiving vitamin d supplements may have a reduced risk of developing type 1 diabetes, while early exposure to cow's milk and cereal proteins may increase risk [15].

**Causes of Type 2 Diabetes Mellitus**
1. MODY (Mature onset diabetes of youth)
2. Pregnancy
3. Acromegaly
4. Cushing syndrome
5. Pheochromocytoma
6. hyperthyroidism
7. mitochondrial mutations
8. insulin gene mutations
9. insulin receptor mutations [16-22].

**OTHER CAUSES OF DIABETES**
1. Genetic mutations affecting beta cells, insulin, and insulin action
2. Down syndrome
3. Klinefelter syndrome
4. Turner syndrome
5. Cystic fibrosis - produces abnormally thick mucus, which blocks the pancreas
6. Hemochromatosis - causes the body to store too much iron. If the disorder is not treated, iron can build up in and damage the pancreas and other organs.
7. Damage to or removal of the pancreas
8. Pancreatitis, cancer, and trauma can all harm the pancreatic beta cells or impair insulin production, thus causing diabetes. If the damaged pancreas is removed, diabetes will occur due to the loss of the beta cells.
9. Endocrine diseases
10. Cushing’s syndrome and acromegaly are examples of hormonal disorders that can cause prediabetes and diabetes by inducing insulin resistance.
11. Autoimmune disorders
   a) Lupus erythematosus
   b) Stiff-man syndrome
   c) Medications and chemical toxins
   d) Nicotinic acid
   e) Certain types of diuretics
   f) Anti-seizure drugs
   g) Psychiatric drugs
12. Drugs to treat human immunodeficiency virus (HIV), can impair beta cells or disrupt insulin action.
13. Pentamidine, a drug prescribed to treat a type of pneumonia, can increase the risk of pancreatitis, beta cell damage, and diabetes
14. Also, glucocorticoids steroid hormones that are chemically similar to naturally produced cortisol may impair insulin action.
15. Many chemical toxins can damage or destroy beta cells in animals, but only a few have been linked to diabetes in humans.
16. For example, dioxin a contaminant of the herbicide agent orange, used during the Vietnam war may be linked to the development of type 2 diabetes. Lipodystrophy is a condition in which fat tissue is lost or redistributed in the body. The condition is associated with insulin resistance and type 2 diabetes.

**PREVALENCE AND INCIDENCE FOR DIABETES MELLITUS**
Diabetes mellitus is a group of metabolic diseases characterized by elevated blood glucose levels.
(Hyperglycemia) resulting from defects in insulin secretion, insulin action or both. Insulin is a hormone manufactured by the beta cells of the pancreas, which is required to utilize glucose from digested food as an energy source. Chronic hyperglycemia is associated with microvascular and macrovascular complications that can lead to visual impairment, blindness, kidney disease, nerve damage, amputations, heart disease, and stroke. In 1997 an estimated 4.5% of the US population had diabetes. Direct and indirect health care expenses were estimated at 98 billion [23]. The type of diabetes is based on the presumed etiology. This chapter provides information about the two most common types of diabetes: Type 1 and Type 2 diabetes (see Table 1).

<table>
<thead>
<tr>
<th>S.No</th>
<th>Characteristics</th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Age</td>
<td>Childhood</td>
<td>Pubertal</td>
</tr>
<tr>
<td>2</td>
<td>Onset</td>
<td>Acute; severe</td>
<td>Mild-severe; often insidious</td>
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<tr>
<td>3</td>
<td>Insulin secretion</td>
<td>Very low</td>
<td>Variable</td>
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<tr>
<td>4</td>
<td>Insulin sensitivity</td>
<td>Normal</td>
<td>Decreased</td>
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<tr>
<td>5</td>
<td>Insulin dependence</td>
<td>Permanent</td>
<td>Temporary; may occur later</td>
</tr>
<tr>
<td>6</td>
<td>Racial/Ethnic groups at increased risk</td>
<td>All (low in Asians)</td>
<td>African Americans, Hispanics, Native Americans, Asian/Pacific Islanders</td>
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<tr>
<td>7</td>
<td>Genetics</td>
<td>Polygenic</td>
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<td>8</td>
<td>Proportion of those with diabetes</td>
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<td>10%-20%</td>
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<td>9</td>
<td>Association: Obesity</td>
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<td>10</td>
<td>Acanthosis nigricans</td>
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<td>11</td>
<td>Autoimmune etiology</td>
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</table>

In type 1 diabetes, the body does not produce insulin, and daily insulin injections are required. Over 700,000 people in the United States have type 1 diabetes; this is 5-10% of all cases of diabetes mellitus. Type 1 Diabetes is usually diagnosed during childhood or early adolescence and it affects about 1 in every 600 children.

Type 2 diabetes is the result of failure to produce sufficient insulin and insulin resistance. Elevated blood glucose levels are managed with reduced food intake, increased physical activity and eventually oral medications or insulin. Type 2 diabetes is believed to affect more than 15 million adult Americans, 50% of whom are undiagnosed. It is typically diagnosed during adulthood. However, with the increasing incidence of childhood obesity and concurrent insulin resistance, the number of children diagnosed with type 2 diabetes has also increased worldwide [24].

For example, from 1982 to 1994 in one mid-western city, the proportion of children with type 2 diabetes increased from approximately 4% to 16%. The prevalence of DM, estimated at 10 percent of persons over the age of 60 years, rises to 16–20 percent among those over the age of 80. The overall prevalence among adults was 7.4 percent in 1995 and is expected to reach 9 percent in 2025.

The annual incidence of type 1 DM in children from birth to 16 years of age varies with ethnicity and is approximately 3–26 new cases per 100,000 persons. For example, among African Americans in San Diego, CA, it is 3.3 per 100,000 and among whites in Rochester, MN, it is 20.6 per 100,000. Approximately 0.3 percent of the population develops the disease by 20 years of age. The annual incidence of type 2 DM is approximately 2.4 per 1,000 persons over age 20. By 65 years of age, 10 percent of the population may have type 2 DM. The prevalence is highest in Native Americans, followed by Hispanics, African Americans, and Asians.

**DIAGNOSIS OF DIABETES**

**Diabetes Testing**

Three blood tests are available to diagnose prediabetes and diabetes:

- Casual plasma (blood) glucose
- Fasting plasma glucose (FPG)
- Oral glucose tolerance test

**Casual Plasma (Blood) Glucose Test**

The criteria for a diagnosis of diabetes with this test is the presence of diabetes symptoms and a blood glucose level of 200 mg/dl or higher.
Fasting Plasma Glucose (FPG) Test
A diagnosis of diabetes is made when the fasting blood glucose level is 126 mg/dL or higher on at least two tests. Values of 100–125 mg/dl indicate prediabetes. A normal fasting blood glucose level is less than 100 mg/dl.

Oral Glucose Tolerance Test
The criterion for a diagnosis of diabetes with this test is a two-hour blood glucose level of 200 mg/dl or higher. Prediabetes is diagnosed if the two-hour blood glucose level is 140–199 mg/dl.

Postprandial Blood Glucose Test
Measures blood glucose levels 2 hours after eating a meal. Postprandial blood glucose is usually done in people who have symptoms of hyperglycemia, or when the results of a fasting glucose test suggest possible diabetes, but are inconclusive. Values of 200 mg/dL or more indicate diabetes.

Hemoglobin A1c (HbA1c), also known as the glycosylated hemoglobin or glycohemoglobin test
It is used to monitor the effectiveness of therapy in people already diagnosed with diabetes. HbA1c measures the amount of glucose attached to hemoglobin (the oxygen-carrying protein in red blood cells), which increases as blood glucose levels rise. Since hemoglobin circulates in the blood until the red blood cells die (half the red blood cells are replaced every 12 to 16 weeks), the HbA1c test is a useful tool for measuring average blood glucose values over the previous 2 to 3 months [27-35].

Purpose of Diagnostics Tests For Diabetes
The fasting, postprandial, and oral glucose tolerance tests are used to diagnose type 1 or type 2 diabetes mellitus.
- HbA1c is used to monitor the effectiveness of dietary or drug therapy in the management of diabetes mellitus.
- To detect hyperglycemia (high blood sugar) and hypoglycemia (low blood sugar).
- To screen for diabetes, a common disease that often does not cause early symptoms.

Chemical Tests
This involves testing the urine with the Benedict’s reagent. Results indicate the person having diabetes based on the color formation.
1. Light color = normal
2. Parrot green color = >120 mg/dl
3. Dark yellow color = >180mg/dl
4. Reddish brown color = +++ > 250 mg/dl
5. Brown color = ++++ > 350 mg/dl

Diasticks
These are strips that used to indicate the person having diabetes mellitus or not. These strips tested with urine and based on the color change only diagnosis the diabetes mellitus.

Glucometers
- These meters are also involving in diagnosing the diabetes mellitus. Within the fraction of seconds these will give results about blood glucose levels.

Other Laboratory Tests
In addition to measures of blood glucose and HbA1c, initial and subsequent doctor visits may include tests to check for kidney damage, a common complication of diabetes. These tests include blood urea nitrogen (BUN), blood creatinine, and protein (albumin) in the urine. The risk of coronary heart disease is increased in people with diabetes, so also need blood tests to measure levels of triglycerides, total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol.

Urine Glucose And/Or Ketones
Patient self-monitoring is easily done with urine dipsticks for detecting and semiquantifying glucose and ketones in urine.

Pathophysiology
Diabetes mellitus is classified on the basis of pathogenesis which causes hyperglycemia and the two broad categories are Type 1 and Type 2 diabetes mellitus. Type 1 diabetes mellitus occurs due to destruction of pancreatic islet β cells, mainly due to an autoimmune process which can cause complete or near total insulin deficiency. Type 2 diabetes mellitus is a progressive, debilitating metabolic blood glucose disorder due to multiple metabolic abnormalities including impaired insulin secretion, insulin resistance, loss of beta cell function, impaired regulation of glucagon secretion and disturbed incretin physiology (Powers 2008, Andukuri et al., 2009). Incretins maintain glucose homeostasis along with other hormones like insulin,
glucagon and amylin. They are released in response to a meal by enteroendocrine cells in the intestine. Incretin dysfunction, along with other defects, has been implicated in contributing to the pathogenesis of type 2 diabetes mellitus (Campbell et al., 2011). A new paradigm of drugs thus have been developed which are based on the actions of the incretins and are injectable long-acting stable analogues of glucagon like peptide-1 (GLP-1) known as incretin mimetics. The classic point of view regarding T1DM pathogenesis was that, in genetically predisposed individuals, some environmental factors may trigger an autoimmune process that leads to β-cell destruction. In the last 4 decades, a dramatic increase in the biochemical identification of islet autoantigens and in the definition of alleles of genes associated with diabetes susceptibility was registered. Nowadays, one considers that genes and environmental factors may have deleterious or favorable effects and, consequently, the immune equilibrium is directed towards aggression or protection. It is the time to recapitulate here the main knowledge we have about the pathogenesis of autoimmune T1DM.

**Pathophysiology of Type 2 Diabetes Mellitus**

To understand the cellular and molecular mechanisms responsible for Type 2 diabetes it is necessary to conceptualise the framework within which glycaemia is controlled. Insulin is the key hormone for regulation of blood glucose and, generally, Normoglycaemia is maintained by the balanced interplay between insulin action and insulin secretion. Importantly, the normal pancreatic cell can adapt to changes in insulin action i.e., a decrease in insulin action is accompanied by upregulation of insulin secretion (and vice versa). Figure illustrates the curvilinear relation between normal cell function and insulin sensitivity. Deviation from this hyperbola, such as in the patients with impaired glucose tolerance and Type 2 diabetes in figure , occurs when cell function is inadequately low for a specific degree of insulin sensitivity. Thus, cell dysfunction is a critical component in the pathogenesis of Type 2 diabetes. This concept has been verified not only in cross-sectional studies but also longitudinally in Pima Indians progressing from normal to impaired glucose tolerance to Type 2 diabetes. However, not only deviation from but also progression along the hyperbola affects glycaemia. When insulin action decreases (as with increasing obesity) the system usually compensates by increasing cell function. However, at the same time, concentrations of blood glucose at fasting and 2 h after glucose load will increase mildly. This increase may well be small, but over time becomes damaging because of glucose toxicity, and in itself a cause for cell dysfunction. Thus, even with (theoretically) unlimited cell reserve, insulin resistance paves the way for hyperglycaemia and Type 2 diabetes.

**Fig 1. Pathophysiology Of Hyperglycaemia And Increased Circulating Fatty Acids in Type 2 Diabetes**
Insulin secretion from the pancreas normally reduces glucose output by the liver, enhances glucose uptake by skeletal muscle, and suppresses fatty acid release from fat tissue. The various factors shown that contribute to the pathogenesis of type 2 diabetes affect both insulin secretion and insulin action. Decreased insulin secretion will reduce insulin signalling in its target tissues. Insulin resistance pathways affect the action of insulin in each of the major target tissues, leading to increased circulating fatty acids and the hyperglycaemia of diabetes. In turn, the raised concentrations of glucose and fatty acids in the bloodstream will feed back to worsen both insulin secretion and insulin resistance.

Obesity
Insulin resistance is strongly associated with obesity and physical inactivity, and several mechanisms mediating this interaction have been identified. A number of circulating hormones, cytokines, and metabolic fuels, such as non-esterified (free) fatty acids (NEFA) originate in the adipocyte and modulate insulin action. An increased mass of stored triglyceride, especially visceral or deep subcutaneous adipose depots, leads to larger adipocytes that are themselves resistant to the ability of insulin to suppress lipolysis. This results in increased release and circulating levels of NEFA and glycerol, both of which aggravate insulin resistance in skeletal muscle and liver (figure 3). Excessive fat storage not only in adipocytes but "ectopically" in non-adipose cells also has an important role. For example, increased intramyocellular lipids are associated with skeletal muscle insulin resistance under some circumstances. The coupling between intrahepatic lipids and hepatic insulin resistance seems to be even tighter.

RISK FACTORS
Risk Factors Of Diabetes Type 1
There aren’t many known risk factors for type 1 diabetes, though researchers continue to find new possibilities. Some known risk factors include:

- **A family history:** Anyone with a parent or sibling with type 1 diabetes has a slightly increased risk of developing the condition.
- **Genetics:** The presence of certain genes indicates an increased risk of developing type 1 diabetes. In some cases — usually through a clinical trial — genetic testing can be done to determine if someone who has a family history of type 1 diabetes is at increased risk of developing the condition.
- **Geography:** The incidence of type 1 diabetes tends to increase as you travel away from the equator. People living in Finland and Sardinia have the highest incidence of type 1 diabetes — about two to three times higher than rates in the United States and 400 times that of people living in Venezuela.

Possible risk factors for type 1 diabetes includes

- **Viral exposure:** Exposure to Epstein-Barr virus, coxsackievirus, mumps virus or cytomegalovirus may trigger the autoimmune destruction of the islet cells, or the virus may directly infect the islet cells.
- **Early vitamin D:** Research suggests that vitamin D may be protective against type 1 diabetes. However, early drinking of cow’s milk — a common source of vitamin D — has been linked to an increased risk of type 1 diabetes.
- **Other dietary factors:** Omega-3 fatty acids may offer some protection against type 1 diabetes. Drinking water that contains nitrates may increase the risk. Consuming dairy products, particularly cow’s milk, may increase infants’ risk of the disease. Additionally, the timing of the introduction of cereal into a baby’s diet may affect risk. One clinical trial found that between ages 3 and 7 months appears to be the optimal time for introducing cereal.

Some other possible risk factors includes

- Having a mother younger than age 25 when she gave birth to you
- Having a mother who had preeclampsia during pregnancy
- Being born with jaundice
- Having a respiratory infection just after birth

Risk Factors of Diabetes Type 2
Researchers don’t fully understand why some people develop type 2 diabetes and others don’t. It’s clear, however, that certain factors increase the risk, including:

- **Weight:** Being overweight is a primary risk factor for type 2 diabetes. The more fatty
tissue you have, the more resistant your cells become to insulin.

- **Fat distribution:** If your body stores fat primarily in your abdomen, your risk of type 2 diabetes is greater than if your body stores fat elsewhere, such as your hips and thighs.

- **Inactivity:** The less active you are, the greater your risk of type 2 diabetes. Physical activity helps you control your weight, uses up glucose as energy and makes your cells more sensitive to insulin.

- **Family history:** The risk of type 2 diabetes increases if your parent or sibling has type 2 diabetes.

- **Race:** Although it’s unclear why, people of certain races — including blacks, Hispanics, American Indians and Asian-Americans — are more likely to develop type 2 diabetes than whites are.

- **Age:** The risk of type 2 diabetes increases as you get older, especially after age 45. That’s probably because people tend to exercise less, lose muscle mass and gain weight as they age. But type 2 diabetes is also increasing dramatically among children, adolescents and younger adults.

- **Prediabetes:** Prediabetes is a condition in which your blood sugar level is higher than normal, but not high enough to be classified as diabetes. Left untreated, prediabetes often progresses to type 2 diabetes.

- **Gestational diabetes:** If you developed gestational diabetes when you were pregnant, your risk of later developing type 2 diabetes increases. If you gave birth to a baby.

**COMPLICATIONS OF DIABETES**

Type 1 diabetes can affect major organs in your body, including heart, blood vessels, nerves, eyes and kidneys. Keeping your blood sugar level close to normal most of the time can dramatically reduce the risk of many complications.

Long-term complications of Type 1 diabetes develop gradually, over years. The earlier you develop diabetes — and the less controlled your blood sugar — the higher the risk of complications. Eventually, diabetes complications may be disabling or even life-threatening.

- Heart and blood vessel disease
- Nerve damage (Neuropathy)
- Kidney damage (Nephropathy)
- Diabetic cardiomyopathy
- Coronary artery disease
- Stroke (Mainly the ischemic type)
- Diabetic myo-necrosis (Muscle wasting)
- Diabetic encephalopathy
- Eye damage
- Foot damage (Diabetic foot)
- Skin and mouth functions
- Osteoporosis
- Pregnancy complications
- Hearing problems.

**TREATMENT OF DIABETES MELLITUS**

The major components of the treatment of diabetes are

A) Drug treatment for diabetes
B) Non drug treatment for diabetes

**A) Drug Treatment for Diabetes**

Anti-diabetic drugs treat diabetes mellitus by lowering glucose levels in the blood. With the exceptions of insulin, Exenatide, and Pramlintide, all are administered orally and are thus also called oral hypoglycemic agents or oral ant hyperglycemic agents. There are different classes of anti-diabetic drugs, and their selection depends on the nature of the diabetes, age and situation of the person, as well as other factors.

Diabetes mellitus type 1 is a disease caused by the lack of insulin. Insulin must be used in Type I, which must be injected or inhaled.

Diabetes mellitus type 2 is a disease of insulin resistance by cells. Treatments include agents which increase the amount of insulin secreted by the pancreas, agents which increase the sensitivity of target organs to insulin and agents which decrease the rate at which glucose is absorbed from the gastrointestinal tract.

**Insulin**

Insulin is usually given subcutaneously, either by injections or by an insulin pump. Research is underway of other routes of administration. In acute care settings, insulin may also be given intravenously. There are several types of insulin, characterized by the rate which they are metabolized by the body. Insulin is essential for the treatment of type 1 diabetes. For many years it was assumed, as an act of faith, that normalizing plasma glucose would prevent diabetic complications. The
diabetes control and complications trial (american diabetes association, 1993) showed that this faith was well placed; type1 diabetic patients were randomly allocated to intensive or conventional management.

**Insulin Sensitizers**

**Sulfonylureas**

Sulfonylureas were the first widely used oral hypoglycemic medications. They are insulin secretagogues, triggering insulin release by direct action on the K\_ATP channel of the pancreatic beta cells.

**Meglitinides**

Meglitinides help the pancreas produce insulin and are often called “short-acting secretagogues.” Their mode of action is original, affecting channels. By closing the potassium channels of the pancreatic beta cells, they open the calcium channels, hence enhancing insulin secretion. Eg: Repaglinide, Nateglinide

**Biguanides**

Biguanides reduce hepatic glucose output and increase uptake of glucose by the periphery, including skeletal muscle. Although it must be used with caution in patients with impaired liver or kidney function, motorman has become the most commonly used agent for type 2 diabetes in children and teenagers. Eg: Metformin, Phenformin, Buformin

**Thiazolidinediones**

Thiazolidinediones (TZDs), also known as “glitazones,” bind to PPAR\_γ, a type of nuclear regulatory proteins involved in transcription of genes regulating glucose and fat metabolism. These PPAR\_γ act on Peroxisome Proliferator Responsive Elements (PPRE). The PPREs influence insulin sensitive genes, which enhance production of mRNAs of insulin dependent enzymes. The final result is better use of glucose by the cells. Eg: Rosiglitazone, Pioglitazone, Troglitazone

**Alpha-Glucosidase Inhibitors**

Alpha-glycosidase inhibitors are “diabetes pills” but not technically hypoglycemic agents because they do not have a direct effect on insulin secretion or sensitivity. These agents slow the digestion of starch in the small intestine, so that glucose from the starch of a meal enters the bloodstream more slowly, and can be matched more effectively by an impaired insulin response or sensitivity. These delays carbohydrates adsorption, reducing the postprandial increase in blood glucose. Eg: Miglitol, Acarbose

**Peptide Analogs**

**Incretin Mimetics**

Incretions are insulin secretagogues. The two main candidate molecules that fulfill criteria for being an incretion are Glucagons-like peptide-1 (GLP-1) and Gastric inhibitory peptide (aqua glucose-dependent Insulin tropic peptide or GIP). Both GLP-1 and GIP are rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4).

**Glucagon-Like Peptide (GLP) Analogs And Agonists**

GLP agonists bind to a membrane GLP receptor. As a consequence of this, insulin release from the pancreatic beta cells is increased. Endogenous GLP has a half life of only a few minutes; thus an analogue of GLP would not be practical. Exenatide, Liraglutide.

**Gastric Inhibitory Peptide (GIP) Analogs**

**DPP-4 Inhibitors**

Dipeptidyl peptidase-4 (DPP-4) inhibitors increase blood concentration of the incretin GLP-1 (glucagon-like peptide-1) by inhibiting its degradation by dipeptidyl peptidase-4 (DPP-4). Vildagliptin, Sitagliptin

**Amylin Analogues**

Amylin agonist analogues slow gastric emptying and suppress glucagons. They have all the incretions actions except stimulation of insulin secretion. As of 2007, primitive is the only clinically available amylin analogue. Like insulin, it is administered by subcutaneous injection.

**B) Non Drug Treatment For Diabetes**

1. **Life style changes which are used to controlling diabetes**

Life style change is defined as the way of living which has been altered by variety manner. Life style have seven principles of good diabetes care:

- Learn as much as you can about diabetes
- Get regular care for diabetes
- Learn how to control your diabetes
- Take care of your diabetic ABC’s
- Monitor your diabetic ABC’s
• Prevent long term diabetes problems
• Get checked for long term problems and treat them

2. Exercise
It is an important in helping to prevent diabetes and is having vital role of our treatment. some good qualities of exercise
1. It helps in losing weight
2. It can reduce blood glucose levels and keep it low for several hours after words
3. Exercise can reduce cholesterol and blood pressure
4. Exercise helps reduce stress

5. Exercise makes the tissues in your body more sensitive to the effects of insulin. This allows insulin to push more glucose out of the blood stream in your cells, which will reduce the level of glucose in our blood.

3. Diet
The diet recommends places an emphasis on foods that are higher in fiber and low in fat. By itself a high fiber, low fat diet can make body more sensitive to insulin. Diet also involves weight loss which is another way to increase diabetic patient’s body sensitivity to the effects of insulin.

REFERENCES
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