AN OVERVIEW ON DIABETES AND ITS MANAGEMENT

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ABSTRACT
Diabetes mellitus is a melancholic disease worldwide with increasing incidence as time passes. Diabetes also accompanies macro-vascular and micro-vascular complications which are due to poorly controlled postprandial hyperglycemia. Prevention appears to be a significant strategy to decrease the affliction of disease. Along with inculcating healthy lifestyle practices across populations, it may be suitable to practice protective pharmacotherapy in those with pre-diabetes and/or other risk factors like obesity, hypertension etc. This review article highlights the old and new approaches to the treatment of diabetes mellitus such as diet modification, oral hypoglycemic medications and also the technologies used in the management of diabetes. A lot of anti-diabetic drugs are currently available, usually, metformin is the first line drug. Other drugs such as sulfonylureas and glinides, pioglitazone, thiazolidinediones, alpha-glucosidase inhibitors, DPP-4 inhibitors, glucagon-like peptide 1- receptor agonist. This review describes the development, prevention and management of diabetes and its complications and suggests practical, evidence-based guidance for their optimal use. This article also aims to summarize the updated recommendations in the diagnosis and management of DM.

KEYWORDS: Diabetes, Management, Diagnosis, Pathogenesis.
INTRODUCTION
Diabetes mellitus, or simply diabetes, is an assembly of diseases characterized by high blood glucose levels that upshot from shortcomings in the body's ability to produce and/or use insulin. Abnormal level of hyperglycaemia gives rise to the risk of microvascular damage (retinopathy, nephropathy and neuropathy). Therefore, it is associated with reduced life expectancy, significant morbidity. It also leads to increased risk of macrovascular complications (ischaemic heart disease, stroke and peripheral vascular disease), and diminished quality of life.

Development of diabetes involves several pathogenetic processes. These include processes, like destructions of beta cells of the pancreas with subsequent insulin deficiency, and others that result due to resistance to the insulin action. The irregularities or deviations of carbohydrate, protein and fat metabolism are due to a deficient action of insulin on target tissues resulting from insensitivity or lack of insulin. The characteristic symptoms of diabetes mellitus may be presented with such as thirst, polyuria, blurring of vision, and weight loss. Often symptoms are not severe or may be absent.

Type 2 diabetes mellitus (T2DM) represents the ultimate stage of a chronic and progressive syndrome representing a heterogeneous disorder caused by various combinations of insulin resistance and decreased pancreatic β-cell function which is then caused by both genetic and acquired abnormalities.\(^1\) Currently, T2DM is diagnosed when the underlying metabolic abnormalities consisting of insulin resistance and decreased β-cell function cause elevation of plasma glucose above 126 mg/dl (7 mmol/L) in the fasting state and/or above 200 mg/dl (11.1 mmol/L) 120 min after a 75-g glucose load.\(^2\)

It is clear that diabetes is characterized by many associated abnormalities. More significantly, they predispose pretentious individuals to severe serious chronic problems. Therefore, it is imperative for medical fraternity to identify “subclinical” diabetes to intercept the disease process.\(^3\) However, the fact that many newly diagnosed type 2 diabetic subjects already suffer from so called “late complications of diabetes” at the time of diagnosis\(^4\) specifies that the diagnosis may have been deferred and, in addition, that the prediabetic condition is detrimental to human health and necessitates improved awareness by physicians and the general public. In type 1 diabetes mellitus the relationship between glycemic control and microvascular complications has been well established.\(^8\)
Prevalence of Diabetes in the world was 5.1% in 2003 and by 2025 is around 6.5%. IGT prevalence in the world was 8.2% in 2003 and to be 9.0% in 2025. (age group 20-79 years). Currently, up to 11% of India’s urban population and 3% of the rural population above the age of 15 have diabetes. The WHO estimates the mortality from diabetes and heart disease cost India about 9450 billion rupees (210 billion $) and expected to increase to 15075 billion rupees (335 billion $) in next 10 years.\(^{[11]}\)

**Signs and symptoms of Diabetes**

The commencement of diabetes is wide-ranging, depending on its precise type. Most Type 2 diabetes cases have a leisurely onset, taking years before the signs start to act. However, in Type 1 cases, predominantly in children, the symptoms may appear rapidly, taking only months or even weeks.

The most apparent signs of diabetes include the following:

- Frequent thirst(*polydipsia*)
- Constant urination(*polyuria*)
- Rapid loss of weight
- Unusual hunger
- Obvious weakness and fatigue

**Diagnosis**

The diagnosis of diabetes mellitus is definitely recognised when a patient presents the typical symptoms of hyperglycaemia and has a random blood glucose value of 200 mg/dL (11.1 mmol/L) or higher, and confirmed on another juncture.

**Pathophysiology**

Pathophysiology of diabetes repos upon knowledge of the basics of carbohydrate metabolism and insulin action. Consumption of food follows carbohydrates break down into glucose molecules in the gut. These glucose molecules are then absorbed into the bloodstream which then elevates blood glucose levels. This rise in glycemic level stimulates insulin secretion from the beta cells of the pancreas. Insulin is required by most cells to allow glucose entry. Insulin facilitates entry of glucose into the cell, by binding to specific cellular receptors. The increased insulin secretion from the pancreas and the subsequent cellular utilization of glucose results in lowering of blood glucose levels. Lower glucose levels then result in lessened insulin secretion.
If production and secretion of insulin are altered by disease dynamics of blood glucose will also change. This decrease in insulin production causes inhibition of glucose entry into cells, therefore resulting in hyperglycaemia. The same effect will be seen if insulin is secreted by the pancreas but is not used properly by target cells. If insulin secretion is increased, blood glucose levels may become very low (hypoglycemia) as huge amounts of glucose enter tissue cells and little vestiges in the bloodstream. Insulin is the only hormone that lowers blood glucose level. The counter-regulatory hormones such as glucagon, catecholamines, growth hormone, thyroid hormone, and glucocorticoids all turn to increase blood glucose levels, in addition to their other effects.\textsuperscript{[12]}

The Role of β-cell in Insulin Resistance

![Diagram of Insulin resistance and β-cell dysfunction]

Insulin resistance and β-cell dysfunction are core defects of type 2 diabetes

Classification of diabetes

Clinical classification

An individual could pass through several phases of glycaemia ranging from normoglycaemia, impaired fasting glycaemia (IFG), impaired glucose tolerance (IGT) to diabetes.\textsuperscript{[16]} The swing between phases could be in both directions depending on the actions of an individual. For example, some individuals may stay in the IGT (impaired glucose tolerance) stage without accomplishing the diagnostic criteria for diabetes whereas others could have acceptable glycaemic control with lifestyle changes in the diabetic stage (Fig.2).
### Aetiological classification

The current aetiolo\_gical classification was proposed by WHO in 1999. Basically, they came to the same conclusion as the American Diabetes Association expert group did in 1997. Type 1 and type 2 diabetes are the two most common categories. Type 1 diabetes is insulin dependent for survival whereas the much more prevalent type 2 diabetes is characterized by defect in insulin secretion, insulin action, or both.

- **Type 1**: Autoimmune or idiopathic β-cell destruction, leading to absolute insulin deficiency.
- **Type 2**: Progressive loss of β-cell insulin secretion on the background of insulin resistance.\[18\]

### Diabetes in Pregnancy (Gestational Diabetes)

**Gestational diabetes** is diabetes found for the first time when a woman is pregnant. Women who are overweight, have had gestational diabetes before or have a strong family history of diabetes are at a higher risk of developing gestational diabetes. Untreated gestational diabetes may cause problems to the baby. Both the mother and the baby are at increased risk for Type II diabetes for the rest of their lives.
Specific types of diabetes
Specific types of diabetes due to other causes, eg. Monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young (MODY), cystic fibrosis and drug or chemical induced diabetes (such as with glucocorticoid use, treatment of HIV/AIDS, or after organ transplantation.

PREDIABETES
Pre-diabetes (comprise of IFG and IGT) is the state that occurs when a person's blood glucose altitudes are higher than normal but not high adequate for a verdict of diabetes. The terms IFG and IGT refer to an intermediate metabolic stage between normal glucose and diabetes. The concept of IFG was introduced by Charles et al. to refer to fasting plasma glucose levels > 6.1 and < 7.8 mmol/L.[35]

Fig. 3: Blood glucose ranges in IFG and IGT patients.

Studies have shown that people with pre-diabetes can avoid or delay the enlargement of type 2 diabetes by up to 58 percent through deviations to their lifestyle that embrace modest weight loss and consistent exercise. For some people with pre-diabetes, intervening early can actually turn back the clock and return elevated blood glucose levels to the normal range.[41]

Pathogenesis of Prediabetes
The progression from normal glucose tolerance to type-2 diabetes is characterized by dual defects that include insulin resistance and an insulin secretory defect caused by beta-cell dysfunction.[Figure-4].
Old and new approaches to Management of diabetes

Diabetes is now ranked as the sixth leading cause of death by disease in the U.S (National diabetes fact sheet, Atlanta 2004). Its treatment, as well as the management of diabetes-related complications, remains a top priority for governments worldwide since the economic burden in 2007 alone exceeded $174 billion.[42]

Pharmacological treatment

Old approaches to the treatment of this chronic progressive disease include diet modification and oral hypoglycemic medications, which have proven inadequate, while insulin therapy only solves the problem temporarily. Even with the newest pharmacotherapy, patients continue to develop macro and microvascular complications. Diabetes is associated with increased cardiac- and stroke-related deaths, kidney failure, blindness, and 60% of non-trauma lower-limb amputations. Apart from insulin treatment, it is possible to gain diabetes control after gastrointestinal bypass surgeries.

Insulin therapy

Insulin is a hormone that treats diabetes by monitoring the amount of sugar (glucose) in the blood. It is derived from either pork (porcine), beef (no longer available in the U.S.), or is genetically made to be identical to human insulin.
Patients with type I diabetes mellitus depend on external insulin (most commonly injected subcutaneously) for their survival because the hormone is no longer produced internally. Patients with type II diabetes mellitus are insulin resistant, have relatively low insulin production, or both; certain patients with Type II diabetes may eventually require insulin if other medications fail to control blood glucose levels effectively.

**The types of Insulin include-**

**Rapid-acting insulin**- This insulin starts working within a few minutes and lasts for a couple of hours.

**Regular- Short acting insulin**- This insulin takes about 30 minutes to work and last for 3-6 hours.

**Intermediate-acting insulin**- This type of insulin takes 2 to 4 hours to work and its effects can last for up to 18 hours.

**Long-acting insulin**- This type of insulin takes 6 to 10 hours to reach the bloodstream, but it can keep working for an entire day.

**Limitations of Soluble Human Insulin**

**Slowly absorbed**

Sub-optimal postprandial glycemic control inconvenient injection timing: 30 min before meals.

**Longer duration of action**- Increased hypoglycaemic risk.

**Lower quality of life**- Injections and meals must be planned.

**Modern Insulin: Definition**

1. Modified or ‘Modern Insulin or Newer Insulin
2. Molecules- differ by one or a few amino acids from the primary structure of insulin
3. Developed- to provide a more physiologic replacement after s.c injection than human insulin
4. Made possible by the advent of Biotechnology- rDNA technology
5. Provide more optimal time-action profiles

**Modern Insulin provides**

1. Meal-time flexibility (Rapid-acting)
2. Superior PPG Reduction
3. Better Glycaemia control
4. Less variability
5. Less Hypoglycaemia
6. Less undesired weight gain
7. Available in Easy-to-use Pens with painless needles

A number of oral medicines are available for treatment of type 2 diabetes as given below:

**Metformin**
Most people who are newly diagnosed with type 2 diabetes will immediately put on a medicine called Metformin. Metformin improves how our body responds to insulin to reduce high blood sugar levels. Common side effects of metformin include nausea, diarrhea and flatulence. Patients with certain types of kidney, liver, and heart disease, and those who drink alcohol excessively should not take metformin.

If the blood sugar levels are still high after two to three months, but your A1C is close to the goal (between 7 and 8.5 percent), a second medicine might be added. The following are general recommendations:
- The most commonly recommended second medicine is a short-acting sulfonylurea, such as glipizide.
- A thiazolidinedione, such as pioglitazone, is an alternative to sulfonylureas, but only for people who are not at increased risk of heart failure or bone fracture.
- A GLP-agonist, such as Exenatide, is an option for patients who are overweight and who want to avoid developing low blood sugar.
- A meglitinide, such as Repaglinide, is an option for people who cannot take a sulfonylurea or prefer to avoid injections.

**Sulfonylureas**
Sulfonylureas work by increasing the amount of insulin what our body makes and can lower blood sugar levels by approximately 20 percent. Sulfonylureas are generally used if metformin does not adequately control blood sugar levels when taken alone. Low blood sugar must be treated quickly by eating 10 to 15 grams of fast-acting carbohydrate (eg, fruit juice, hard candy, glucose tablets).
Thiazolidinediones
This class of medicines includes Pioglitazone, which works to lower blood sugar levels by increasing the body's sensitivity to insulin.
Common side effects of thiazolidinediones include:
- Weight gain and swelling of the feet and ankles.
- A small but serious increased risk of developing or worsening heart failure. People who take thiazolidinediones should monitor for swelling.
- A small increased risk of bone fractures.

The GLP-agonists
Dulaglutide and Liraglutide, are injectable medicines. They are not a first-line treatment but might be considered for people whose blood sugar is not controlled on the highest dose of one or two oral medicines. They may be especially helpful for overweight patients, who are gaining weight on oral medicine.

DPP-IV Inhibitors
This class of medicines includes Sitagliptin, Saxagliptin, and Vildagliptin. They lower blood sugar levels by increasing insulin release from the pancreas in response to a meal. They are not a first-line treatment, but they can be given alone in patients who can’t tolerate the first-line medicines (metformin, sulfonylureas), or they can be given with other oral medicines if blood sugars are still higher than a goal.

Meglitinides
Meglitinides include Repaglinide and Nateglinide. They work to lower blood sugar levels, similar to the sulfonylureas and might be recommended in people who are allergic to sulfabased drugs.

Alpha-glucosidase inhibitors
Which include Acarbose and Miglitol, work by interfering with the absorption of carbohydrates in the intestines. This helps to lower blood sugar levels, but not as well as metformin or the sulfonylureas. They can be combined with other medicines if the first medicine does not lower blood sugar levels enough. [44]
Innovative Diabetes Pipeline

These new classes of drugs that have entered the market or are expected to enter the market include:

- Glucagon-like peptide-1 (GLP-1) agonists;
- DPP-IV inhibitors;
- PPAR agonists;
- Sodium-glucose co-transporter
- (SGLT) inhibitors;
- Cannabinoid CB1 receptor antagonists;
- Glucokinase activators (GKA);
- Other novel agents

![Fig. 5: Melissa Zebrowiski: Report: Innovations in the management of DM, Business insights 2008.](image)

Non-pharmacological treatment

Health care providers should advise all diabetics not to initiate tobacco and emphasize on stopping smoking as utmost priority for diabetic smokers, since it increases the risk of renal failure, visual impairment, foot ulcers, leg amputations and heart attacks in people with diabetes. The incidence of micro and macrovascular complications was significantly augmented in smokers compared to non-smokers. As worries alcohol, consumption of large amounts can cause hypoglycaemia and this can occur many hours after alcohol intake, mainly if no food has been consumed beforehand.[45]
**Innovations that are changing the way we control diabetes**

It's been around a century since researchers\(^{[46]}\) discovered a way to treat diabetes. Since then, there have been a quantity of medical and technological developments that aim to make the lives of people living with diabetes - both type 1 and type 2 more controllable. Around the globe, the group of disorders affects 371 million people worldwide, a number that's expected to increase to 552 million by 2030.\(^{[47]}\) From monitoring blood sugar levels - a challenging experience that people with diabetes must grow used to doing every day - to ways that make insulin easier to distribute, here are some of the innovations that are making diabetes management more convenient.

**Medtronic created the world's first 'artificial pancreas.'**

In September 2016, the FDA approved (48) a device that's often referred to as an "artificial pancreas" for use in people with type 1 diabetes over age 14. The device, made by Medtronic, is called the MiniMed 670G, and it works by robotically monitoring a person's blood sugar levels and governing insulin as needed. No constant checking and injecting is required with
this device. That way, it can act like a pancreas, the organ in our bodies that in healthy people is able to moderate our blood sugar levels by pumping out insulin that can process the sugars found in food.\cite{55}

**A glucose monitor that can get software updates just like your phone.**

![Glucose meter](image)

Fig. 7: Glucose meter.\cite{55}

A glucose monitor that can receive software updates, eliminating the need for people to constantly upgrade to new glucose meters when the technology advances.

**A tube-free insulin pump, are working on a tube-less artificial pancreas.**

![Tube free insulin pump](image)

Fig. 8: Tube free insulin pump.\cite{56}

Insulet, a company that makes a tubeless insulin pump called the Omnipod, started its first artificial pancreas clinical trials in September, partnering with the continuous glucose monitor
company Dexcom. The Omnipod itself first launched back in 2005, and the company's hoping to get the artificial pancreas on the market by 2018. Unlike other devices, Insulin's would go directly on the body and sync with a wireless controller. The device would deliver up to three days worth of insulin.

➤ **Timesulin built an insulin pen that can tell us when we last took a dose**

![Timesulin's insulin pen](image)

**Fig. 9: Timesulin’s insulin pen.**[56]

For people living with Type 1 diabetes and some people living with Type 2, injecting insulin is a necessary part of life. Some choose to get insulin through a pump, but others inject either from a vial or using a pen. So, along with his brother, John Sjolund, who has lived with Type 1 diabetes for more than 30 years, founded Timesulin, a company that makes a pen cap that tracks our last insulin dose.[56]

**Glucose monitoring lens**

![Glucose monitoring lens](image)

**Fig. 10: Glucose monitoring lens.**[57]
The device is the latest attempt to develop a needle-less blood sugar monitor for diabetics. In September 2016, Alphabet's Verily and Sanofi announced a spinoff company called Onduo that's tasked with helping diabetics find easier ways to live their lives and treat the disease.

**Prevention and management of diabetes complications**

Diabetes is a group of chronic diseases characterized by hyperglycaemia. Modern medical care uses a vast array of lifestyle and pharmaceutical interventions aimed at preventing and controlling hyperglycaemia. In addition to ensuring the adequate delivery of glucose to the tissues of the body, treatment of diabetes attempts to decrease the likelihood that the tissues of the body are harmed by hyperglycaemia.

The consequence of defending the body from hyperglycaemia cannot be overstated; the direct and indirect effects on the human vascular tree are the major source of morbidity and mortality in both type-I and type-2 diabetes.

**CONCLUSIONS**

It is essential to raise awareness about diabetes and its escalating rates around the world. That is the reason why the International Diabetes Federation and the World Health Organization started the International Diabetes Day. It is celebrated on 14th November to mark the birthday of Frederick Banting who, along with Charles Best, was instrumental in the discovery of insulin in 1922, a life-saving treatment for diabetes patients.

There are old and new approaches to the treatment of diabetes mellitus. Old approaches include diet modification and oral hypoglycemic medication. Insulin is a temporary solution to the problem. In addition, insulin therapy has serious complications, such as diabetic ketoacidosis etc. Non-insulin diabetes treatment engages incretin mimetics, which the substances found in the stomach and the intestinal tract as a response to food intake. Then, they signal the release of insulin from the pancreas. There are the oral hypoglycemic agents, such as sulphonylureas and similar (secretagogues), biguanides (sensitizers), thiazolidindiones, alpha glucosidase inhibitors, and incretine-analogues/agonists. It is possible to undergo metabolic surgery, gastric bypass in particular. Biological drugs can also help fight diabetes mellitus.
Diabetes has reached epidemic proportions in India
Many drugs available but unmet need persists
Numerous drugs in the pipeline but long-term safety & efficacy needs to be evaluated
However, each patient is unique, thus individualize treatment

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