

REVIEW ARTICLE

EVOLUTION OF MANAGEMENT OF DIABETES MELLITUS

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Introduction:

Diabetes is an ancient disease and for centuries extreme diets and herbal remedies were used to treat diabetes symptoms. The discovery of insulin in 1921 transformed the landscape of diabetes treatment and was followed by the discovery of several new therapies which improved glycemia and increased patient life span.

In the 1990s, the DCCT and the UKPDS trials demonstrated that tight glucose control reduced the microvascular complications of diabetes, but had marginal effects on cardiovascular disease, the leading cause of death in patients with diabetes. In 2008, the FDA directed that all new diabetes medications demonstrate cardiovascular safety.

Developments in diabetes technology like continuous glucose monitoring systems, insulin pumps, telemedicine and precision medicine have advanced diabetes management.

Today type 2 diabetes is preventable and long-term remission of diabetes is possible. Progress continues in the field of islet transplantation, perhaps the ultimate frontier in diabetes management.

Epidemiology: According to the World Health Organization (WHO) approximately 537 million adults (ages 20–79 years) are living with diabetes today, and this number is predicted to rise to 643 million by 2030 and 783 million by 2045¹.

History:

The first description of a polyuric state resembling diabetes has been attributed to Hesy Ra, chief physician to the Egyptian Pharaoh Djoser, nearly 5000

years ago². The presence of sweetness in the urine was initially noted by the ancient Hindu physicians Charaka and Sushruta around 400–500 BC². The term “diabetes” (from the Greek for siphon) has been attributed to Apollonius of Memphis in ancient Greece (around 250 BC). John Rollo, a Scottish military surgeon is said to have first used the word “mellitus” (from the Latin for honey) in 1797².

Treatment of diabetes in preinsulin era:

3000 BC to 1920: The treatments in ancient time were empirical and included Herbs, chemicals, Opium, meat diets and starvation “Keto” diet.² In the mid-1600s, Thomas Willis introduced carbohydrate-restriction and limited his patients to a diet of milk and barley water boiled with bread. In the 1700s, the “Meat Diet” was popularized by John Rollo.² The French physician Apollinaire Bouchardat (1809–1886), considered the “Father of Diabetology,” became the first to implement individualized therapy for patients, introducing exercise, and advocating daily urine testing “to keep track of the tolerance and to guard against a return of sugar without the patient’s knowledge³. Around the end of the nineteenth century, Sir William Osler (1849–1919), the “Father of Modern American Medicine,” recommended that diabetes patients consume a diet of 65% fat, 32% protein, and 3% carbohydrate, and abstain from “all fruits and garden stuff³. At the dawn of the twentieth century, Frederick Allen of The Rockefeller Institute introduced a diet that involved fasting for up to 10 days to clear glycosuria, followed by a restricted-calorie diet that provided mainly fat and protein (especially eggs) with the smallest amount

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of carbohydrates (mostly vegetables) necessary to sustain life. This regimen essentially starved people with severe diabetes to control the disease. Elliot P. Joslin, the pioneer of diabetes care in the United States (US), embraced the Allen approach, but also used a treatment that began by withdrawing only fat and then protein after 2 days followed by a progressive lowering of carbohydrates in the diet to 10 g a day or until the patient's urine was free of sugar!

Discovery of insulin and the era of Glucose

Lowering drugs:

20th century

Insulin: In 1921: Banting, Best, Macleod and Collin discovered insulin. In 1940s: Longer acting insulin introduced. Included among these was NPH insulin (1946), still in use today, other one is Lente insulin

Oral agents:

In 1955, the first oral anti-diabetic medication, secretagogues the sulfonylurea (SU) carbutamide was introduced, followed by others in the same family including chlorpropamide, tolbutamide, glipizide, glyburide and glimiperide among others⁵. The first insulin sensitizer, the biguanide Metformin was introduced in Europe in 1957 and in the US in 1995. In the mid-1990s, several oral anti-diabetic agents were introduced including the alpha-glucosidase inhibitors (Acarbose, Miglitol and Voglibose), followed by the meglitinides (Nateglinide and Repaglinide)⁵, secretagogues, structurally different from SUs and of shorter duration action. The late 1990s and early 2000s saw the introduction of the thiazolidinediones (TZDs), which are PPAR α agonists and potent insulin sensitizers⁵. Rosiglitazone was withdrawn but Pioglitazone is still available, with proven benefits for stroke prevention and diabetes prevention

21st century:

With the turn of the twenty-first century, the range of anti-hyperglycemic options broadened to include the first human insulin analogs followed by several other short- and long-acting analogs, pramlintide (an injectable amylin analog) in 2005, and the dipeptidyl-peptidase inhibitors (DPP-4 inhibitors) which are oral agents in the incretin class of drugs in 2006. These medications (Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin, Alogliptin) inhibit DPP-4 activity, increase endogenous incretin levels, and thereby promote glucose-dependent increases in insulin and inhibit glucagon secretion. Other drugs launching in the late 2000s include colesevelam (a bile acid sequestrant which activates liver farnesoid receptors, lowers glucose by increasing incretin secretion and improving beta cell function) in 2008. Bromocriptine which activates

and reset hypothalamic dopamine receptors was introduced in 2009.

Drugs with (cardiovascular) CV benefit:

2008 FDA directate all diabetes drugs should demonstrate CV safety^{9,8}. Perhaps the most important classes of drugs to be introduced in the 2000s are the GLP-1 receptor agonists (GLP1-RA), the SGLT2-inhibitors (SGLT2i) and the dual GLP-1 receptor and GIP receptor agonists (GIP/GLP1-RA)⁵. The GLP1RA (Exenatide, Liraglutide, Lixisenatide, Albiglutide, Dulaglutide and Semaglutide) directly act on the GLP-1 receptor to stimulate glucose-dependent insulin secretion and inhibit glucagon secretion. Their effects are far more potent than those of the DPP-4 inhibitors. In addition, they also reduce postprandial glucose excursions by slowing gastric motility and act centrally to increase satiety, leading to weight loss⁵. In 2022, the FDA approved the first combined GIP and GLP-1RA for the treatment of adults with type 2 diabetes (T2DM), with initial studies demonstrating superiority in both glycemic control and weight loss compared to GLP1-RA alone⁷. The SGLT2i drugs act through a novel mechanism to inhibit SGLT2 transporters in proximal renal tubules promoting glucosuria and lowering of blood glucose⁵. The robust cardio-renal benefits of these medications have transformed the landscape of diabetes treatment⁸, and led to these agents being recommended for cardio-renal risk reduction in high risk patients with T2DM⁹.

Antidiabetic drugs and their efficacy:

Insulin and the GLP-1RA and dual GLP-1RA/GIP-RA have *very high efficacy*; TZDs, SUs and metformin *high efficacy*; SGLT2i *intermediate to high efficacy*; and DPP-4i, AGI and colesevelam *intermediate efficacy*⁹

Cardiovascular Outcomes Trial (CVOT)s and Cardio-renal Protection:

In the 1990s, the DCCT and the UKPDS trials demonstrated the benefits of tight glucose control on the microvascular complications of diabetes such as retinopathy, nephropathy and neuropathy. However, tight glucose control had marginal effects on macrovascular disease. FDA guidance in 2008, directing that any new diabetes therapy be evaluated for CV safety⁶. Following the FDA guidance, several large cardiovascular outcomes trials (CVOTs) were conducted and results with the GLP-1RA and SGLT2i have transformed the landscape of diabetes treatment¹⁰. In 2015, the EMPA-REG OUTCOME trial demonstrated that empagliflozin, compared to placebo, significantly reduced the incidence of major adverse cardio-vascular events (MACE) comprising non-fatal MI, stroke and CV death in patients with T2DM and

established CV disease¹²The first positive CV results with GLP-1RA were reported in the LEADER trial with liraglutide¹³and have been subsequently confirmed as a class effect with albiglutide (HARMONY study) and dulaglutide (REWIND study). In the CVOTs to-date, the GLP-1RA have consistently demonstrated reduction in atherosclerotic cardiovascular disease (ASCVD)¹¹ events in patients both with and without established ASCVD, however, their effect on renal disease is confined to improvements in albuminuria without preventing progression to end stage kidney disease (ESRD—dialysis/kidney transplant) ESRD¹⁴. Further, the GLP-1RA do not have beneficial effects on HF in diabetes (REF). In contrast, the SGLT2i have modest benefits on atherosclerotic MACE confined to patients with established ASCVD¹⁴ but have robust benefits on reducing hospitalization for HF and progression of renal disease, regardless of existing ASCVD or a HF history. More importantly, unlike GLP-1RA, SGLT2i reduce hospitalization for HF and progression to ESRD in those with and without diabetes, as seen in the DAPA HF, DAPA CKD, CREDENCE and the EMPEROR PRESERVED/REDUCED studies.¹² The above cardio-renal benefits have led to a major shift in international treatment guidelines. Both the American Diabetes Association (ADA) and the European Society for the Study of Diabetes (EASD) now recommend the use of SGLT2i and GLP-1RA as first-line treatment to reduce the risk of cardiorenal complications in individuals at high risk of CV disease, irrespective of metformin use and baseline/target glucose control¹³. The European Society of Cardiology (ESC) guidelines also recommend either a SGLT2i or a GLP-1RA as first-line treatment in people with T2DM at high CV risk, ahead of metformin¹⁴. However, it is important to note that in the CVOTs, most participants with diabetes were on at least one glucose-lowering medication (primarily metformin) at baseline¹⁵.

Prevention of Diabetes mellitus:

1. Da Qing study :The first large study to demonstrate that T2DM can be prevented was the Da Qing study from China published in 1995¹⁶. The authors randomized 577 men and women with impaired glucose tolerance (IGT) to the active intervention (n=438) or control (n=138). At 6 years, the cumulative incidence of diabetes was 67.7% in the control group compared with 43.8% in the diet group, 41.1% in the exercise group, and 46.0% in the diet-plus-exercise group (P<0.05).
2. Finnish Diabetes Prevention study :The next large study which evaluated diet and lifestyle in diabetes prevention was the Finnish Diabetes Prevention study (2001) which randomized 522 subjects with IGT (172 men and 350 women; mean age, 55 years; mean BMI 31 kg/m²) to either the intervention or the control group¹⁷. The intervention group received individualized counseling aimed at reducing weight and dietary fat intake, and increasing fiber intake and physical activity. The cumulative incidence of diabetes after four years was 11% in the intervention group and 23% in the control group, with a relative risk reduction of 58% (p <0.001).
3. US Diabetes Prevention Program (DPP, 2002) also evaluated the role of metformin in diabetes prevention¹⁷. In this study, pre-diabetic individuals (68% women, mean age 51 years, mean BMI 34 kg/m²) were randomized to placebo, metformin (850 mg twice daily), or a lifestyle-modification program targeting a minimum 7% weight loss and 150 min of physical activity per week. After an average follow-up of 2.8 years, as compared to placebo, lifestyle intervention reduced the incidence by 58% compared to only 31% with metformin.
4. Indian Diabetes Prevention-1 (IDDP -1) study, in which 531 subjects with IGT (421 men, 110 women, mean age 45.9 years, BMI 25.8 kg/m²) were randomized into four groups^{17,18}. Group 1 was the control, Group 2 was given advice on lifestyle modification (LSM), Group 3 was treated with metformin (MET) and Group 4 was given LSM plus MET. After 3 years, the cumulative incidences of diabetes were 55.0%, 39.3%, 40.5% and 39.5% in Groups 1–4, respectively. Thus, in this study, although both lifestyle and metformin significantly reduced the incidence of diabetes in Asian Indians with IGT, surprisingly, there was no added benefit from combining them.

The Concept of Diabetes Remission:

It is well known that intensive diet and lifestyle measures can lead to significant weight loss which may be sustained for long periods of time and lead to a regression from overt diabetes to normal glucose regulation in individuals with T2DM¹⁹.

Remission should be defined as a return of HbA1c to < 6.5% (<48 mmol/mol) that occurs spontaneously or following an intervention and that persists for at least 3 months in the absence of usual glucose-lowering pharmacotherapy

Intensive Weight Management & Diabetes Remission

1. Intensive weight management in routine primary care: The DiRECT study in the UK assessed whether intensive weight management within routine primary

care increased remission of T2DM in patients diagnosed within the past six years and not on insulin²⁰. In an open-label, cluster-randomized trial, 306 individuals (20–65 years) were randomized to an intervention group (n = 157) that underwent total diet replacement (825–853 kcal/day formula diet for 3–5 months), progressive food reintroduction (2–8 weeks), and structured support for long-term weight loss maintenance, or a control group (n = 149). Mean bodyweight by 10.0 kg versus 1.0 kg and diabetes remission was achieved in 46% vs 4% of participants in the intervention versus control group, respectively.

2. Bariatric Surgery and Diabetes Remission: compared to intensive diet/lifestyle, more robust rates of diabetes remission are achieved after bariatric surgery, with Roux-en-Y gastric bypass (RYGB) being associated with greater remission rates than sleeve gastrectomy. In a large retrospective, observational study of 5928 patients with T2DM at the time of surgery, over an average follow-up of nearly 6 years, 71% of patients experienced remission of T2DM (mean time to remission 1.0 year), with weight loss after bariatric surgery being strongly associated with initial T2DM remission up to a threshold of 20% total weight loss.

3. Pharmacologic Treatment and Diabetes Remission: In the SURPASS-1 trial 705 individuals with short duration T2DM (mean 4.7 years, mean HbA1c~8.0%) were randomized to placebo or escalating doses of tirzepatide a novel “twincretin” with glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist activity, recently approved by the FDA for the treatment of type 2 diabetes²¹. After 40 weeks of treatment, the mean HbA1c decreased from baseline by ~ 2.0% in the tirzepatide group, along with weight loss of 7 to 9.5 kg from a baseline of 5.5 kg. Notably, more participants on tirzepatide than on placebo met HbA1c targets of <7.0% (~ 90% vs 20%) and 6.5% or less (81–86% vs 10%) and 31–52% of patients on tirzepatide versus 1% on placebo reached an HbA1c of less than 5.7%, which is in the normal range.

Technology and Diabetes Management

1. Advances in Glucose Monitoring and Insulin Delivery
CGM and Insulin pump: introduction of sophisticated continuous glucose monitoring systems (CGMS) which not only provide near-real-time glucose readings, but also communicate with state-of-the-art insulin pumps which correlate insulin delivery with glucose trends.

Insulin pump: Hybrid closed-loop systems partially automate insulin dosing, requiring only manual mealtime boluses and occasional correction boluses.

This has led to significant improvements in glucose control and reductions in hypoglycemia.

TIR (Time in range): Is a new diabetic metric that expresses the percentage of time of a person with diabetes spend within their target of glycemic range. In registry and case-control longitudinal data, pump use has been associated with fewer CV events and reduction of CV disease and all-cause mortality.

Artificial pancreas: Studies on bi-hormonal (insulin and glucagon) systems are also ongoing.

Insulin pumps and CGMS are expensive and primarily used in patients with type 1 diabetes mellitus (T1DM). The goal in this field is to develop long term, implantable glucose sensors and fully automated insulin delivery systems which use artificial intelligence to seamlessly maintain glucose in the normal range without the need for human intervention.

The Advent of Telemedicine:

Telemedicine can be useful for the management of diabetes mellitus and can also be cost-effective²³. However, it must be remembered that although telemedicine can be used to deliver effective diabetes care and complement current diabetes management strategies, it cannot replace all in-person consultations. Patients with complex health needs, and those who require a physical examination are not suitable for telemedicine.

AI (artificial intelligence): Together with diabetes technology and telemedicine, the use of artificial intelligence (AI)²² is slowly coming of age and may soon present a paradigm shift in diabetic management through data-driven precision care

Precision Medicine:

Precision medicine²⁴ is an emerging approach for disease prevention and treatment that considers how individual variability in genes, environment, and lifestyle impact disease. This is in contrast to a one-size-fits-all approach, in which disease treatment and prevention strategies are developed with less consideration for the differences between individuals. Compared with oncology, the role of precision medicine in diabetes management is less clear given the heterogeneous nature of T2DM, and the fact that diabetes medications are usually selected based on comorbidities, cost and side effects, rather than on the specific pathophysiology underlying disease in the individual patient.

The Last Frontier- Islet Transplantation in Diabetes Management

Islet Transplantation

A promising avenue is α -cell replacement through whole pancreas or islet cell transplantation²⁵. This approach not only restores physiologic insulin secretion but also reduces hypoglycemia risk by partially restoring glucagon secretion.. Unfortunately, donor shortage hinders the widespread implementation of these therapies.

Stem cell technology:

The advances in stem cell technology may be able to bridge this gap of donor shortage in transplantation technology in the future.^{25,26}

Conclusion:

Treatment of Diabetes was started with starvation .With advent of breakthrough discoveries of Insulin, oral antidiabetic agents and technologies diabetes treatment has been revolutionized. The improvements in glycemic control with medical therapy and lifestyle measures have clearly ameliorated polyuric symptoms and increased the life span of patients with diabetes. However with increased life expectancy, patients are more prone to manifest the classic microvascular and macrovascular complications of diabetes, broadening the goal of diabetes treatment to include prevention of these long-term complications. Drugs Dietary adjustment & Discipline in life remains at the centre of diabetes management .Individualized good compliance and surveillance by the care giver can only help to achieve this.14 th November has been promulgated as” World diabetes day(WDD)” by UN resolution 61/225 in 2006.WDD is the world’s largest diabetes awareness campaign reaching a global audience of over 1 billion people in more than 160 countries. The campaign draws attention to issues of paramount importance to the diabetes world and keeps diabetes firmly in the public and political spotlight.

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