Review Article:

Discovery, treatment and management of diabetes

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Abstract:

The history of diabetes started in Egypt, Arab and Asia 3,500 years ago. From the 16th - 18th century diabetes has been diagnosed and treated more methodically starting in Europe but the remedy for the diabetes was only discovered in the last century. Discovery of insulin for the treatment of diabetes represents one of the major humanitarian and scientific milestones of the 20th century. But health care providers have no awareness of the history of diabetes. Knowledge of the history provides a better understanding of contemporary issues and a clearer vision for the future. Ancient physicians recorded their observations in an attempt to better understand the nature of the ailment, its origin, and treatment. Diabetes was recognized in antiquity but its history has been characterized by numerous cycles of discovery, neglect and rediscovery.

Key words: Diabetes, history, treatment and management

Background:

Diabetes is a chronic disorder affecting carbohydrate, fat and protein metabolism due to defective production and action of the hormone insulin characterized by hyperglycemia. Typically people with diabetes have a long term risk of developing progressive disease such as blindness, end stage renal disease, heart disease, cerebro-vascular disease, and peripheral vascular disease as well as peripheral neuropathy. In fact there is hardly any organ system or tissue that is spared by diabetes mellitus [1].

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The prevalence of the diabetes mellitus is increasing rapidly and standing as a major threat to mankind. There are about 100 million (3% of world population) diabetic patients in the world today [2,3]. By the year 2025, 6.3% of the global population will have diabetes (334 million). Each year 6 million people develop diabetes [4]. It is now recognized as the third leading cause of death in adults after heart disease and cancer [5].

A remedy for diabetes was discovered in the 20th century though diabetes mellitus was first described 3500 years ago. The discovery of insulin for the treatment of diabetes represents one of the major humanitarian and scientific milestones of the 20th century [6]. However health care providers receive very little information on the history of diabetes during their training. Historical concepts of causes and the nature of diabetes have a vital role to play if we are to understand and deal with the current diabetes epidemic. In addition there is only sparse literature available on the history of diabetes. Thus the present work was undertaken to compile a comprehensive history on diabetes.

History of diabetes:

The history of diabetes is divided into four periods that reflect the understanding and management of the disease in different historical periods [7].

1. Ancient period

2. Diagnostic period

3. Experimental period

4. Discovery of Insulin

Ancient period:

This period was witness to the first clinical description and complication of diabetes mellitus by Egyptian physicians 3,500 years ago who had been striving to diagnose and treat diabetes. Egyptian medicine influenced the medical practices of neighboring cultures; including the culture of ancient Greece [8]. From the first century AD, the Greeks described the disease as "a melting down of the flesh and limbs into urine [8]. Hippocrates did not specifically mention diabetes in his writing but his disciples, Galen and Aretaeus contributed much to the description of diabetes [9]. Around 250 BC Apollonius of Memphis probably coined the name "diabetes" from Ionian Greek. The literal translation, is "to go through" or siphon, reflecting the early understanding of a disease that drained patients of more fluid than they could consume [8]. Aretaeus of Cappadocia first used the term diabetes in the 2nd century AD and he concluded that it was due to a fault in the kidney, a generic description for conditions that are instantly recognizable today. Galen (AD 131 – 201), a Roman physician, proposed the same notion but he used an alternative term for diabetes including "diarrhea urinosa"- excessive urinary output, and "dipsakos" - excessive thirst and drinking [7].

Dating from the 5th – 6th centuries AD, Sushruta and Charuka, two notable Indian physicians, first reported a sweet tasting substance (Madhumeha) present in the urine of patients with polyuria, being sticky to touch and strongly attracting ants [7]. Indian description of this time appear to distinguish two forms of diabetes one affecting older, fatter people and the other thin people who did not survive long, that resemble the present day subdivision of type I and type II diabetes [10]. At the same time, Chinese (Chen Chuan) and Japanese (Li Hsuan) physicians also described the sweetness of diabetic urine, which apparently attracted dogs. Their recommended treatments included the avoidance of wine, sex and salty cereals [7].

That diabetic urine tasted sweet was subsequently emphasized by Arabic Medical

Texts during the 9th – 11th centuries, when Arabic medicine was at its peak of achievement. Avicenna (AD 960 - 1037) described accurately the clinical feature of diabetes and mentioned two specific complications of the disease namely "gangrene" and "fall down" of sexual function. He recommended treatment of a mixture of lupin, fenugreek and zedoary seeds that possess mild hypoglycemic activity [11].

Diagnostic period:

From the 16th to 18th century the diabetic medicine falls into the diagnostic period and was recognized as a separate disease entity centred largely in Europe [7]. In the 16th century, the Swiss physician Von Hohenhein (Paracelus) suggested that diabetic urine contains white powder, due to deposition of salt in the kidney that causes thirst. It was not until the 17th century that Thomsas Wills (1674), a physician and anatomist describing diabetes as the 'pissing evil', made reference to the sweet taste of diabetic urine and reiterated the same observation that was first discovered in Asian and Hindu writings over 1000 years before [12]. Thomas Sydenham then proposed that diabetes was a systemic disease. Mathew Dabson (1776) finally indicated that the sweet substance in urine is sugar, and that it is not present in the kidney but in serum.

In 1809, John Rollo, an apothecary and chemist, first used the term "mellitus", the Latin and Greek root for honey and documented excess sugar in the blood as well as urine [8]. He differentiated diabetes mellitus from a polyuric disease which is tasteless (Insipidus). He also concluded that diabetes causes cataract and an odor of acetone (decaying apples) on the breath of some patients. He treated his patients with meat rich carbohydrate restricted diet, and sometimes supplemented this with an anorectile compound including antimony, opium and digitalis like the starvation diet of Allan and others a century latter [5]. In the last part of the 18th century Thomas Cawley described that diabetes may follow damage to the pancreas [7].

Experimental period (Mid to late 19th century):

During this period the glucoregulatory role of the pancreas became clear, and the biochemical mechanism was recognized. Knowledge of diabetes and its associated effect on metabolism dramatically improved in this era [7].

Claude Bernard (1813-1878) believed that the sugar present in diabetic urine was stored in the liver as glycogen. He also found that the central nervous system was involved in controlling blood glucose concentration while stimulating vagal motor nuclei by pricking the medulla of rabbits

with a needle [7]. In 1869, Paul Langerhans (1847 – 1888), aged 22, while working for his doctorate in Berlin noticed small clusters of cells in the pancreas. Langerhans simply described these structures without speculating as to their possible function. In 1889, Osker Minikowski and Joseph Von Mering who were assistants of Albert Naunyn, the foremost European clinician in diabetes in Strassburg at that time, removed the pancreas from dogs to discover whether it had an effect on blood sugar levels. After the operation, dogs unexpectedly displayed typical signs of severe diabetes with polyuria, polyphagia, thirst, wasting and death in ketoacidotic coma. This observation firmly established the role of pancreas in diabetes [13].

It was only in 1893 that Edouard Laguesse (1861 – 1927) suggested that these clumps of cells in pancreas might constitute the endocrine tissue of the pancreas, which he named the Islets of Langerhans (named after Paul Langerhans) [7]. This theme was continued further by the Belgian physician, Jean de Meyer, who in 1909 isolated glucose lowering hormone from the pancreas and gave it the name insulin (Latin, insula= Island, as it was produced by islet cells [14].

Discovery of insulin:

As soon as the link between the pancreas and diabetes was recognized, researchers focused on treating diabetes with pancreatic extracts. Several workers including Georg Ludwig Zülzer (Germany), Nicolas Paulesco (Romania), EL Scott and Isael Kleinter (North America) were actively trying to search for the active principal of insulin. In the early 1900s, Zülzer experimented with pancreatic compounds and made an injection called "acomatrol" into a dying diabetic patient. The patient improved but later died when Zülzer's acomatrol supply was exhausted [14]. Later, in 1911, a European pharmaceutical company funded a small laboratory and some workers to help Zulzer, who took out an American patient on his "Pancreas Preparation Suitable for the Treatment of Diabetes". But Zulzer's laboratory was turned over to the military during World War 1 [14].

In the early years of 20th century purification, removal of toxic products and demonstrations consisting of biological activity were the principal problem. Professor John James Rickard Macleod, a physiologist at the University of Toronto, continued to pursue his work on carbohydrate metabolism. In 1921, Frederick G. Banting was hired and Charles Herbert Best, a 21 year old student was recruited for assisting Banting, who proved that it is an active substance of the pancreas that is associated with hypoglycemia in diabetic dogs under Macleod's patronization. James Bertram Collip, a biochemist, later joined the team, and improved the extraction and purification of insulin. The most important demonstration was that the pancreatic extract enabled the diabetic liver to store glycogen and it could clear ketouria[7]. Discovery of insulin for the treatment of diabetes represents one of the major humanitarian and scientific milestone of this century. It was a momentous advance in medicine [7].

Insulin testing:

On 1 January 1922, the insulin extract made by Banting and Best was first injected into Leonard Thompson, a 14 year old boy who weighed only 64 pounds, dying of diabetes in Toronto Hospital. Leonard was given a 5 -10 mL injection in each buttock. But it failed to relieve the symptoms. Abscesses developed at the injection sites, and Leonard became even more acutely ill. However, his blood glucose level dropped initially. On 23rd January another insulin extract injection refined by Collip reduced Thompson's blood sugar to normal (from 520-120 mg/dL) in about 24 hours and abolished his glycosuria and ketonuria. He began to gain weight and regain strength. Leonard lived a relatively healthy life for 13 more years but died of pneumonia at the age of 27 [8].

About the time that insulin was being developed, the treatment of diabetes was centered on starvation [14]. Frederick Allen, the leading American diabetologist, believed that since the diabetic's body could not use food, he limited the amount of food to his patients to reduce the strain. The outcome was better than ever seen before for type II diabetes, but for those with type I, death from "inanition" was not uncommon. Fortunately, Allen's treatment did allow a number of young people to survive to become the first insulin users [15].

Allen's treatment was so rigid that he put one of his patients named Elizabeth Evans Hughes on diet. This diet almost lead to starvation, and she hated these "nightmares" during her treatment period. But Elizabeth clung to life until Banting agreed to see her in August 1922 [15].

Banting was astonished to see the girl, who weighed only 45 pounds and was scarcely able to walk, was still alive. He began insulin at once, injecting 1 mL twice daily and increasing her calorie allowance by 100 calories each day. Elizabeth went on to live a happy and productive life. She did not tell anybody about her diabetes not even her future husband until after they became engaged. Elizabeth probably had about 43,000 insulin injections before she died suddenly of a heart attack at age 60 [15]. Her recovery was hailed around the world as a true medical miracle.

Nobel Prize and politics:

Interestingly, after the successful use of insulin isolated by Leonard Thompson, Collip, who had agreed to share all information with Banting and Best, but he decided not to tell them how he had improved the insulin extraction. Because he was thinking about patenting his refined insulin himself. This led to an unsavory encounter (a physical fight actually) between Banting and Collip. A cartoon published at the time, and unfortunately now lost, showed Banting sitting on Collip, choking him. The caption read "The Discovery of Insulin" [15].

Though, insulin was discovered by the team of four, the credit for the discovery of insulin is given to Banting and Macleod who won the Noble Prize in 1923. In an attempt to remedy this injustice Banting publicly acknowledged Best's role in the discovery of insulin and Banting shared the prize money equally with Best while Macleod agreed to do the same with Collip [7].

Although conflicts were resolved sufficiently to allow the four key players to continue their work, Banting lost trust in his coworkers and eventually began to withdraw from the team. Privately and bitterly, the men feuded over priorities and who did what for the next two decades [9].

Life of four heroes:

Macleod died in 1935 in Scotland [8] while Banting immediately reached heroic proportions in the medical community and among the general public. He later became the Head of the Research Institute at Toronto University. Banting died in a plane crash in Newfoundland in 1941. Best outlived everyone in this drama, dying in 1978 after a distinguished career at the University of Toronto, where he eventually took over Macleod's job [5]. Collip also achieved recognition for his pioneering work in purifying insulin [15].

Further development:

Within a year of the first successful extraction, insulin was sufficiently purified for therapeutic administration to patients with diabetes mellitus. Chemical identification of insulin was first prepared by Abel in 1926 [16]. In 1928, Wintersteiner and his colleagues described insulin as a protein composed of amino acids [17]. Fredrick Sanger et al. proposed the structure of insulin that consists of two protein chains connected by a disulfide bond in 1945 [19] and sequenced the protein of insulin in 1955 [17]. In 1958, Sanger was recognized with a Noble Prize in chemistry [20]. The major breakthough in the development of insulin was the development of the radioimmunoassay for insulin level measurement by Rosalyn Sussman Yalow and Solomon Berson in 1959. This work was also rewarded with the Nobel Prize [21]. The chemical synthesis of the A and B chain of insulin and the combining of a synthetic and natural chain of the active insulin was achieved by Du et al. (Germany), Katsoyanis (USA) and Kung (China) in1963 [17]. Proinsulin was first synthesized by Donald Steiner et al. in 1967 [22]. However, the total synthesis of human insulin, starting from peptides with intact disulfide bridges was achieved by Sieber and his colleagues at Ciba Geigy laboratory in Basel in 1974 [23]. For many years, beef/pork insulin was the only source of insulin. The first commercial product of human insulin was developed by recombinant DNA technology in 1979 by Goeddel et al. [23], and human insulin was first prepared by Graham Bell et al. in 1980 [24]. DNA technology, which freed manufacturers from the demands of collecting huge stockpiles of animal pancreatic tissue allowed synthesis of a "human" type of insulin. In July 1996 the Food and Drug Administration approved the first recombinant DNA human insulin analogue, Lispro (Humalog). At present, more than 300 insulin analogues have been identified, including about 70 animal,, 80 chemically modified , and 150 biosynthetic insulin preparations [25].

Classification of diabetes:

In 1939, Himsworth reported that some patients required higher insulin doses to lower their blood glucose concentration. This observation laid the foundation for the concept of impaired insulin action, which is now known to be a crucial factor

in pathogenesis of non insulin dependent diabetes mellitus (NIDDM). However, in 1979, Deborah Doniach and GianFranco Battazo suggested that autoimmune attack directed against ß cell mass causes Insulin dependent diabetes mellitus (IDDM) [7]. Another type of diabetes occurs only during pregnancy (gestational diabetes) predisposing to type II diabetes [26].

The diabetic control controversy:

After the discovery of insulin many physicians felt that tight control of diet along with insulin was of paramount importance in managing the deadly disease of diabetes. Other practitioners however believed that with the advent of insulin using specific diets as treatment could be liberalized [12]. Considering the value of loose or tight control led to a long term prospective clinical trial with insulin, oral hypoglycemic agents and diet by the University Group Diabetes Programme (UGDP) in 1970. But this study failed to show that the "improved control" prevented or slowed the development of complications [27].

A decade later, the National Institute of Diabetes, Digestive and Kidney Diseases developed a study called the Diabetes Control and Complications Trail (DCCT) by insulin therapy only on patients with type 1 diabetes. In 1993 the results of the DCCT reported that intensive control of the blood sugar over a 7 year study interval reduced the progression of diabetic complications retinopathy, nephropathy and neuropathy but also resulted in a threefold increased risk of serious hypoglycemia. The relationship between the control and complications in type 2 diabetes was also evaluated by United Kingdom Prospective Diabetic Study (UKPDS). Following an average decade of follow up on 5,000 newly diagnosed patients, the study concluded that a 1% decrease in glycosylated Haemoglobin A_{1c} causes a 35 % reduction of microvascular complications. These two studies at the end of the 20th century gave physicians and patients a solid confirmation of the benefit of good control and thus ending the nearly 50 years of divisiveness and confusion [12].

Traditional medicine for managing diabetes:

Spices, herbs and indigenous plants have been used for treating diabetes in Egypt, India, and China from thousands of years ago [28]. Plants with sufficient evidence for blood glucose level lowering activity in diabetes include: onion [29], garlic [30], jamon (*Eugenia Jambolana*) [31], neem, methi (*Trigenella foenum grceum*), Karela (*Memordica Chantia*) and Kalonji (*Nigella sative*) [28]. Oral administration of the aqueous extract of the whole *Ocimum sanctum* plant is beneficial against the development of insulin resistance in fructose fed rats [32].

In 1923, Collip found that onion has a hypoglycemic effect in fasting and depancreatized animals [33]. Histopathological findings suggested that some of these plants also increased the number of B cells in experimental animals [34]. Hypoglycemic medicinal plants are about 75 per cent as active as the synthetic medicine 'Tolbutamide' [35]. Medicinal plants are cheap, easily available and have no additional side effect at all [36], and thus might be considered as another choice in treating diabetes.

Oral hypoglycemic agents:

An oral drug is a far more convenient and comfortable way instead of delivering insulin. Among the millions of type 2 diabetes, about 40 % use insulin , 50% use oral agent and 10% use a combination of two [8]. The first oral hypoglycemic agent was discovered serendipitously in 1942 by M.J. Janbon, Professor of Pharmacology, while working on sulfonylurea for typhoid disease in Montpellier in France. He asked August Loubaieres, Professor of Medicine to try this agent on diabetic patients. Sulfonylurea produced an undoubted fall of blood glucose but it was ineffective in animals after pancreactomy. Ten years later, Franke and Fuchs in Berlin rediscovered the sulfonylurea as oral hypoglycemic agent and applied it clinically [12].

Other oral agents followed with the biguanide, metformin succeeding over phenformin due to its side effect, lactic acidosis. Glucosidase inhibitors became more widely used in the 1980s.The thiazolidinediones were introduced in the 1990s, although troglitazone was rapidly withdrawn for its hepatic toxicity. However, pioglitazone and rosiglitazone are now in widespread use. Recent additions include non sulfonylureas repaglidine and nateglinide similar to sulfonylureas but have a short half-life [12].

In late 2005, Emisphere initiated a 90-day Phase II study to evaluate the efficacy and safety of fixed

doses of oral insulin in patients with type 2 diabetes [37].The National institute of Health (NIH) has launched a nationwide clinical study to determine whether oral insulin (capsule of insulin crystals) can prevent or delay onset of type I diabetes [8]. The oral insulin trial failed to prevent type 1 diabetes in at-risk people. The European Nicotinamide Diabetes Intervention Trial (ENDIT) also failed to prevent or delay type 1 diabetes with nicotinamide, a vitamin present in small amounts in a normal diet. Another NIH oral insulin clinical trial was conducted with more close supervision under Type 1 Diabetes TrialNet, a collaborative network of more than 100 medical centers across the United States, Canada, Finland, United Kingdom, Italy, Germany, Australia and New Zealand that came into existence for the prevention of type 1 diabetes and preserving insulin production in new-onset patients [38]. The first trials were started in 2003. One Trial Net study sought to turn off the immune attack on beta cells with Rituximab, a monoclonal antibody that binds to and temporarily destroys a specific class of immune cells. Another under way study is testing whether mycophenolate mofetil (MMF) or MMF plus daclizumab (DZB), drugs approved by FDA to prevent rejection after an organ transplant, can slow or arrest the autoimmunity of type 1 diabetes [39].

Life expectancy of people with diabetes:

Prior to advent of insulin, most patients with diabetes died shortly after diagnosis but the good news is that we have learned a lot about the value of careful control in diabetes management over the past 85 years. The recently conducted Diabetes Control and Complications Trial (DCCT) provided information about how to maintain near-normal blood glucose levels and lower the risk of complications by almost 75% [9].

Life expectancy of people with diabetes has increased. In 1897, the average life expectancy for a 10-year-old child diagnosed with diabetes was 1 year. Diagnosis at age 30 carried a life expectancy of 4 years, while a 50-year-old with a new diagnosis could expect to live 8 more years. By 1945, a newly diagnosed 10-year-old had a 45-year life expectancy; a 30-year-old had 30 or more years, and a 50-year-old 15 and more years to live. Today's life expectancy for people with diabetes is still lower than that for the general population by about 15 years but better control is leading to longer and healthier lives [40].

The discovery and therapeutic application of insulin in the 1920s was a miraculous development in the treatment of diabetes that enabled individuals affected by this disease to live an almost-normal life. Type II patients could control blood glucose with diet and exercise, and increase their life expectancy [41]. As people began to live longer, they experience complications that had not previously been seen. People with diabetes are at increased risk for the development of serious complications, including blindness, kidney failure, heart disease, stroke, and amputations [9].

Latest development:

Great strides were made in insulin pump technology, and implantable pumps are now an option for some patients. A new class of medications called insulin sensitizers, which stimulate a gene to produce more insulin-controlled proteins, has been released. These proteins remove glucose from the bloodstream, essentially improving the availability of insulin. It also decreases the body's glucose production [8].

Pancreatic or islet cell transplantation is also under way for type I diabetes [8].

The U.S. Food & Drug Administration (FDA) approved the first inhaled insulin Exubera or insulin human (rDNA origin) inhalation in January 2006 for both type 1 or type 2 diabetes. Inhaled insulin is one of the greatest breakthroughs for people who must take short-acting insulin [42,43].

Oral-Lyn is an oral spray formulation of human insulin indicated for the treatment of type 1 and 2 diabetes. Generex Biotechnology started it clinical use of Oral-Lyn in type 2 diabetics in Ecuador in 2005 [44].

Taiwan scientists Sung et al. reported the success in early tests of an oral insulin solution in diabetic rats [45]. They bundled insulin with chitosan -- a chemical derived from the shells of shrimp, crabs and lobsters into tiny particles called nanoparticles. They then put these nanoparticles in an oral solution, which they tested on diabetic male rats. Laboratory tests showed that the insulin reached the rats' blood stream and lowered their blood glucose levels [45].

Conclusion:

This historical review shows that the most of advancement in discovery, treatment and management of diabetes have occurred in the 20th century and that has given the greatest benefit to mankind in the form of longer life. In 20th century much of the morbidity and mortality of diabetes has been reduced by discovery of insulin and aggressive treatment with diet and exercise. Effective use of oral insulin is the target of the21st century. Perhaps one day, injecting insulin will become a thing of the past. Clinical trials on medicinal plants may be put to thought for alternative oral medication. However, increased understanding of the pathophysiology of diabetes with continuous advancements in the prevention and treatment of diabetes and its complications may cure diabetes through genetic corrections before they emerge in 21st century.

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