

Historical View of Diabetics Mellitus: From Ancient Egyptian Polyuria to Discovery of Insulin

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Abstract

History is the pioneer of all researches and developments, and the history of diabetes has its beginnings in antiquity about over three millennia. Diabetes mellitus is one of the oldest diseases from the human civilization. Also it is one of the most studied diseases in the history of medicine. Main symptoms of this disease are hyperglycaemia, excessive thirsty, increased appetite, gradual loss of body weight, and continuous passing of huge honey-sweet urine that often drew ants. The disease causes either for inadequate insulin production, or for the body cells do not respond properly to insulin, or both. Descriptions of diabetes mellitus have been found in the Egyptian Papyri, in ancient Indian and Chinese medical literature, and in the works of ancient Greek and Arab physicians. In the 17th century works of Thomas Willis; in the 19th century, the glycogenic action of the liver is done by French physiologist Claude Bernard; famous experiment of removing the pancreas from a dog and producing severe and fatal diabetes are performed by Oskar Minkowski and Joseph von Mering; and finally in the 19th century, isolation of insulin from pancreatic islets is done by Frederick Banting and Charles Best to save diabetes patients from the suffering from diabetes. These are the roots of all achievements in favor of welfare of diabetes patients. At present the prevalence of diabetes is very high worldwide, and is increasing day by day. In this study historical points of diabetes are highlighted for the awareness of this disease.

Keywords: Dibatics, Papyrus Ebers, ancient period, history, insulin, treatment

1. Introduction

Diabetes mellitus (DM) is a metabolic disease that is characterized by hyperglycemia due to defects in insulin secretion, insulin action or a combination of both (Karamanou, 2016). The long-term effects of diabetes are damage, dysfunction, and failure of various vital organs (Alam, 2017). There are mainly two types of diabetes mellitus: Type 1 diabetes (T1D), which is insulin dependent, and type 2 diabetes (T2D), which is non-insulin dependent (International Diabetes Federation, 2017). The pancreas contains β -cells that release a hormone called insulin, which helps to move the glucose from the blood into the cells (Goodpaster, 2010). Diabetes patients bear high blood sugar and some other common symptoms are increased urination, increased thirst, increased hunger, unusual weight loss, blurry vision, fatigue, cuts and bruises that do not heal, etc. (WHO, 2002; Mohajan & Mohajan, 2023).

In 2019, diabetes caused 4.2 million deaths, and 463 million adults aged between 20 and 79 years old are living with diabetes that costs \$720 billion per year for diagnosis, treatment, and social consciousness purposes. It is expected that diabetes will be the 7th leading cause of death by 2030, and patients may rise up to 700 million by 2045 (Galicia-Garcia et al., 2020). About 30 minutes or more of moderate to vigorous aerobic exercise, such as brisk walking, biking, swimming, jogging, running, etc. per day; a total of at least 150 minutes a week can

reduce weight successfully, and helps in diabetes controlling process (Goodpaster, 2010). Healthy balanced-diet, such as foods high in fiber, vegetables, fruits, etc. can reduced fatality of the disease (Schellenberg et al., 2013).

We have found various descriptions in ancient history about diabetes, such as in the Egyptian Papyri, in ancient Indian and Chinese medical literature, as well as in the work of ancient Greek and Arab physicians (Ghalioungui, 1987). In Egyptian medicine book named *Ebers Papyrus* describes condition resembling diabetes, with its copious flow of urine about in 1550 BC (Sattley, 1996). In the 2nd century, the Greek physician Aretaeus of Cappadocia described the clinical presentation of diabetes in some details (McGrew, 1985).

In the 6th century, there was a close interconnection between religion, medicine, and astrology in India. The diagnostic aspect of medicine was relatively highly developed. Indian physician Sushruta and the surgeon Charaka have worked on diabetes. They thought that diabetes is a hereditary, and associated with obesity, indolence, lethargy and overindulgence in sweets, rich foods and milk products, and the treatment was involved with dieting and purging (Duke, 1991).

Our modern approach to diabetes started when Thomas Willis, added the term “mellitus”, Latin for “honey sweet” (McGrew, 1985). In 1776, Matthew Dobson found that diabetes increases the problems of the kidney. He proofed that the sweetness of the urine was due to sugar, and consequently, discovered hyperglycemia. He forwarded that the diabetes was a systemic disease, rather than one of the kidneys (Dohson, 1776). In 1869, Paul Langerhans found small clusters of unusual cells in the pancreas (Gill, 1990; Ahmed, 2002).

In 1889, Oskar Minkowski and Joseph von Mering discovered that a pancreatectomy produced high diabetes in a dog (von Mering & Minkowski, 1890). In 1921, Canadian physician Frederick Grant Banting and American-Canadian medical scientist Charles Herbert Best have discovered insulin, which is extensively used for diabetes treatment (Banting et al., 1922). At the Nobel Prize accepting lecture Banting says “*Insulin is not a cure for diabetes, it is a treatment*”. The discovery of insulin had an enormous impact on the life of diabetic patients (Forsham, 1982).

2. Literature Review

The literature review is an introductory section, where seminal works of previous researchers are given priority (Polit & Hungler, 2013). It deals with a secondary research source and does not thinks about coming research works (Gibbs, 2008). It helps the researchers to understand the subject, and it serves as an indicator of the subject that has been carried out previously (Creswell, 2007). Konstantinos Laios and his coauthors show that Aretaeus of Cappadocia has been given accurate description of diabetes more than that of any other physician of antiquity, who is able to elaborate upon earlier texts enriching them with his own original findings and numerous thoughtful reflections (Laios et al., 2012).

Bernardo Alberto Houssay has highlighted the works of Joseph von Mering and Oskar Minkowski who have discovered that diabetes occurs in the absence of the pancreas, which leads to the discovery of insulin and its application to the treatment of patients suffering from diabetes (Houssay, 1952). Sazid Alam and his coworkers depicted preliminary opinion that diabetes was associated to an alimentary illness, and concluded with the discovery of it being a persistent systemic ailment and described three successive ways (Alam et al., 2017).

Marianna Karamanou and her coworkers have tried to introduce historical background of diabetes mellitus and have attempted to highlight the development of their current knowledge for the welfare of the diabetes mellitus patients. They have started their research works from the ancient Egypt to isolation of insulin from pancreatic islets by Frederick Banting and Charles Best (Karamanou et al., 2016). Ignazio Vecchio and his coauthors have provided a comprehensive overview of insulin discovery, including recent advancements, such as personalized and individualized insulin therapy (Vecchio et al., 2018). Devajit Mohajan and Haradhan Kumar Mohajan have tried to show that a balanced diet and an increase of the level of physical activity can help to maintain a healthy weight, staying healthier for longer and to reduce the risk of diabetes (Mohajan & Mohajan, 2023).

3. Research Methodology of the Study

Research is an essential and influential device to the academicians for the leading in academic disciplines (Pandey & Pandey, 2015). Methodology is a recommendation to accomplish a good research (Kothari, 2008). It tries to describe the types of research and the types of data (Somekh & Lewin, 2005). Research methodology is a strategy for planning, arranging, designing, and conducting a meaningful and valuable research, which tries to develop logic to generate theory within which the research is conducted (Remenyi et al., 1998; Legesse, 2014).

A good researcher must describe her/his ontological, epistemological, and methodological assumptions properly. Ontology is the branch of philosophy that studies concepts, such as existence, being, becoming, and reality (Hofweber, 2020). Epistemology is the philosophical study of the nature, origin, and limits of human knowledge (Annis, 1978). At the beginning of the main discussion we have consulted on the nature of diabetes in ancient period, then we have discussed on the diabetes of pre-insulin diagnostic period. We have tried to highlight the

role of pancreas for the development of diabetes. Finally, we have tried to discuss about pre-insulin, insulin, and post-insulin periods.

To prepare this article we have taken the help from the secondary data sources. The valuable materials of this paper are collected from the published papers, research reports, published books and notebooks, internets, websites, etc. Throughout the study we have consulted them unsparingly (Mohajan, 2020).

4. Objective of the Study

The topmost objective of this paper is to consult about the history of diseases mellitus. Some other minor objectives of the study are as follows:

- to show the nature of diseases in ancient period,
- to provide the diagnosis during pre-insulin period, and
- to highlight the discovery of insulin and its effects.

5. Ancient Period

The disease diabetes has apparently plagued human for a very long time. About 3500 years ago the ancient Egyptians have explained the clinical aspect alike to diabetes mellitus (Ebbell, 1937). In Egypt, back to 1550 BC the first written on diabetes in the *Eberes Papyrus* (which is a 110-page scroll, and about 20.23 meters long and 30 centimeters in height) is polyuria, which is similar to diabetes, and now we call it type 1 diabetes (T1D) (Bryan, 1930; Veiga, 2010). Eberes Papyrus is the first accurate descriptive riveting medicine document, and is discovered by Egyptologist George Eberes in Thebes in 1872 that reveals an astonishing medical sophistication in the Nile valley about 3500 years ago (Loriaux, 2006; Dupras et al., 2010). It is considered likely to have been compiled from more ancient copies, contains 877 prescriptions. For the treatment of a condition of “*too great emptying of the urine*”, ancient Egyptian physicians were advocating the use of wheat, grains, bones, fruit, grit, green lead, earth, and sweet beer (Ebeid, 1999).

Around 230 BC, Apollonius of Memphis probably for the first time used the term “diabetes”. The first entire clinical explanation of diabetes, which often called “*Cicero medicorum*” for his elegant Latin, is found in the monumental eight-volume work of Aulus Cornelius Celsus (25 BC-50 AD), entitled *De Medicina* of Roman encyclopaedist. It is one of the best sources concerning medical knowledge in the Roman world (Zajac et al., 2017). Greek physician Hippocrates (460 BC), father of medicine, did not specifically mention diabetes in his writings; but there are reliable materials with the sign and symptoms of diabetes, such as excessive urinary flow with wasting of the body (Sanders, 2002; Alam, 2017).

The term “*diabetes*” from Greek-Siphon or “*diabainein*” which means “*passing through*” or “*to run through*” or “*Siphon*”, was first time coined by famous Greek physician Aretaeus of Cappadocia (81-133AD) in Asia Minor, for the patients who passing too much urine like a siphon. He spoke of diabetes as “*the mysterious sickness*”. Although clear and complete description of diabetes was made by Aretaeus; but none he and other physician of ancient Greek were able to treat the disease effectively (Laio et al., 2012).

Roman physician, surgeon and philosopher Aelius Galenus (129-216AD) observed that diabetes was a rare ailment as he had seen only two cases during his clinical observation (Vivian, 1973). He mentioned the development of diabetes is due to weakness of the kidney and gave it names “*diarrhea of the urine*” and the thirsty disease “*dipsakos*” (Alam et al., 2017). In ancient China, during “*the Chinese Hippocrates*” Chinese pharmacologist, physician, inventor Chang Chung-Ching (150-219) has described polyuria, polydipsia, loss of weight, and sweet urine which attracted by insects are symptoms of a specific disease (Kraft, 1998).

Ancient Indian physician Sushruta and the surgeon Charaka (400-500 BC) described sweet taste of urine, noting that ants congregated round it, and being sticky to the touch; in polyuric younger patients and named it as “*madhumeha*” or honey urine (Singh et al., 2010). They mention that diabetes affects primarily the rich castes and is related to the excessive food consumption, such as rice, cereals, and sweets. They further observed and noted in their writings that the disease was most prevalent in those who were indolent, overweight and gluttonous, and who indulged in sweet and fatty foods. They have provided physical exercise and liberal quantities of vegetables as a treatment of obese patients, and a nourishing diet for lean patients (Tattersall, 2010). Sushruta, in his work Samhita, identified two types of diabetes; one affecting older, fatter people and the other thin people who did not survive long, later to be named type-I and type-II diabetes (Champaneria et al., 2014).

The treatment of diabetes in ancient times hardly contributed to an improved quality of life. Byzantine Greek physician and medical writer Aetius Amidinus (6th century) prescribed a cooling diet, diluted wine, and cooling applications to the loins as a treatment. In 650, Paul of Aegina prescribed a remedy of pot-herbs, endive, lettuce, rock-fishes, juices of knotgrass, elecampane in dark colored wine and decoctions of dates and myrtle to drink in the first stages of the disease (Savona-Ventura, 2002).

In the 7th century, Chinese physician Chen Chuan recorded the sweet urine and named the disease “*Hsiao kho ping*” with symptoms, such as intense thirst, copious drinking and large amounts of urine which is tasted sweet. Another physician of China, Li Hsuan noted that the patients with diabetes were prone to boils and lung infections. As a treatment of this disease his colleague physician Li Hsuan prescribed avoidance of wine, salt, and sex (Peumery, 1987). During the 8th century, physicians observed the tendency of diabetic patients to develop skin infections as furuncles, rodent ulcers, and troubles of the eyesight (Karamanou et al., 2016).

Persian physician Ibn Sina (Avicenna) (980-1037), who has termed the disease “Al-dulab” means wheel of water and “Zalqul Kulliyya” means diarrhea of the kidneys in medical encyclopedia in *The Canon of Medicine* (Ghalioungui, 1987). He is the first author able to write the differentiating nature of diabetes associated with emaciation from other causes of polyuria (Eknoyan & Nagy, 2005). He accurately described the clinical features of diabetes and mentions two specific complications of the disease, such as gangrene and the “collapse” of sexual function (MacFarlane, 1990). Ancient remedies for diabetes were “oil of roses, dates, raw quinces and gruel, jelly of viper’s flesh, broken red coral, sweet almonds and fresh flowers of blind nettles” (Lakhtakia, 2013).

6. Pre-Insulin Diagnostic Period

Swiss physician, alchemist, lay theologian, and philosopher Aureolus Theophrastus Bombastus von Hohenheim, better known as Paracelsus (1493-1541) reports that diabetic urine contains an abnormal substance which remains as a white powder after evaporation that is due to the deposition of salt in the kidneys, causing ‘thirst’ of the kidneys and polyuria. Therefore, he describes that diabetes is a constitutional disease that “irritates the kidneys” and provokes excessive urination (Kirchhof et al., 2008).

In 1674, Thomas Willis (1621-1675), a personal physician to King Charles II of England and a physician at Guy’s Hospital in London, added the adjective “mellitus” means “honey” to the term diabetes that means “siphoning off sweet water” to indicate the sweet taste of urine. He defined diabetes mellitus as the “Pissing Evil.” He could determine whether his patients had diabetes or not by sampling their urine. This method of monitoring blood sugars goes on largely unchanged until the 20th century (Willis, 1674). English physician Thomas Sydenham (1624-1689) has speculated that diabetes is a systemic disease arising in the blood (Weber & Mayer, 2020). In 1776, the Liverpool physician, natural philosopher and experimental physiologist Matthew Dobson (1735-1784) published a paper that was the first description of hyperglycemia, confirmed that sugar was present in both the urine and blood of diabetic patients. He suspects that diabetes may be a systemic disease (Dobson, 1776; MacFarlane, 1990).

In 1788, Thomas Cawley discovered correlation between shriveled pancreas and diabetes after the careful observation of the people with pancreatic injury developed diabetes (Cawley, 1788). In 1797, John Rollo, surgeon general to the Royal Artillery, started treatment of polyuria for the first time through the dietary restrictions. In 1798, he reported a dietary approach to diabetes involving carbohydrate restriction that is a system destined to persist to modern times (Rollo, 1797; Ahmed, 2002). His diet greatly improved glycosuria, which supports that diabetes is a “peculiar affection of the stomach”. Hence, he is therapeutically correct, but wrong in conception (Gill, 1990).

During the 19th century physicians remain busy to describe symptom complexes and the natural history of the disease (Jaeger, 1869). In 1815, the French chemist Michel Chevreul (1786-1889) proved that the sugar in diabetic urine was glucose (Chevreul, 1815). In 1848, German chemist, Hermann von Fehling (1812-1885) developed quantitative test for glucose in urine, which is known as Fehling’s solution (Medvei, 1993). In 1857, French physiologist of Sorbonne University Claude Bernard (1813-1878) hypothesized that glycogen is stored by the liver, and demonstrated that the liver could produce glucose from glycogen, and release it into the blood. He is considered as the “father of carbohydrate metabolism”. Between 1846 and 1848, he reported that glucose was present in the blood of normal in animals, even when starved. He also found higher concentrations of glucose in the hepatic than in the portal vein. He believes that overproduction of glucose may be the cause of diabetes (Olmsted, 1953; Young, 1957).

In 1857, English chemist, physician, and natural theologian William Prout (1785-1850) was the first to describe diabetic coma. At the same year Czech physician Wilhelm Petters (1824-1889) demonstrated the presence large amounts of acetone in the urine of diabetes patients. Adolf Kussmaul (1822-1902) proposed that acetonemia was the cause of diabetic coma (Matteson & Kluge, 2003). In 1869, Eduard von Jaeger (1818-1884) is credited with the first description of diabetic retinopathy in his seminal work *Atlas of Diseases of the Ocular Fundus* (Jaeger, 1869). In 1871, M. Troiser observed that diabetes in patients with hemochromatosis, naming it “bronze diabetes” (Medvei, 1993).

7. Diabetes and Pancreas

In 1869, German pathologist, physiologist and biologist Paul Langerhans (1847-1888) refined the specific role

of the pancreas, and discovered the anatomical site of insulin production. He performed detailed microscopic studies, and demonstrate that clusters of cells that are not in connection with the ducts carrying digestive juices to the gut. He also admitted that he is “*not able to explain the nature and function of these cells*”. He described the unique morphologic features of the pancreatic islands that were subsequently named after him “*Islets of Langerhans*” that contains the β -cells, which secrete insulin directly into the bloodstream (Langerhans, 1869).

Leading American diabetologist, Frederick Madison Allen (1879-1964) believed that, since diabetes patients could not utilize the food efficiently, limiting the amount of food would improve the disease (Ramachandran & Viswanathan, 1998). He provided “*Allen Diet*”, which was a carbohydrate-restricted low-calorie diet. But the dietary restriction treatment was harsh and death from starvation was not uncommon in patients. He was known for pioneering the “*starvation diet*” (Bliss, 1982). In 1885, Frederick Pavy (1829-1911), physician the Guy’s Hospital, gave a description of neuropathic symptoms. In 1889, German physician and physiologist Oskar Minkowski (1858-1931) and German physician Joseph von Mering (1849-1908) performed their famous experiment of completely removing the pancreas from a dog (pancreatectomy) and producing severe and fatal diabetes. Actually their work was not related to diabetes, but aimed to see if the pancreas was vital for life (von Mering & Minkowski, 1890).

The French pharmacist and hygienist Apollinaire Bouchardat (1809-1886), considered as the modern father of diabetology, observed an improvement of diabetic patients during the German siege of Paris in 1870. He showed that fasting was a method to reduce glycosuria, and speculated that the principal cause of diabetes was located in the pancreas. He stressed the importance of exercise, and developed a procedure for self-testing urine to determine the presence of glucose. He developed a low carbohydrate diet for his diabetic patients (Harris, 2013). Later, German pathologist and physician Bernhard Naunyn (1839-1925), became famous for advising sugar-free diets, known as the “*Bouchardat’s treatment*” (Colwell, 1968).

In 1893, French investigator Edouard Hedon (1863-1933) made a very important contribution and showed that the total pancreatectomy was necessary for the development of diabetes (Bliss, 2007). In 1893, French pathologist and histologist Gustave Edouard Laguesse (1861-1927) has suggested that pancreatic islet cells are involved in diabetes, which had been discovered in 1869 by the 22-year-old Paul Langerhans, and named them the Islets of Langerhans. In 1894, Russian born medical doctor and researcher Moses Barron (1884-1974) linked damaged Islets of Langerhans to the cause of diabetes (Laguesse, 1893).

In 1907, German internist, Karl Harko von Noorden (1858-1944) proposed that the thyroid, pancreas, adrenals and parathyroids controlled carbohydrate metabolism (von Noorden, 1907). In 1909, English physiologist Eugene L. Opie (1873-1971) reported hyaline degeneration of the islands in diabetic patients and named it insulin (Opie, 1901). In 1916, American physician and pathologist Edward Sharpey-Schafer (1850-1935) has suggested that the islands of Langerhans produced a glucose regulating hormone that he termed insulin.

8. Insulin Period

Insulin is a peptide hormone that is produced and released by β -cells of the pancreatic islets, which finely tunes the metabolism of carbohydrates, fats, and protein inducing the uptake of glucose from the blood into fat, liver, and skeletal muscle cells (Vecchio et al., 2018). Prior to insulin discovery, diabetes treatment mostly consisted of starvation diets (Ramachandran & Viswanathan, 1998). The discovery of insulin has been a milestone and has truly revolutionized both the therapy and the prognosis of the diabetes (Vecchio et al., 2018). In 1906, German physician George Ludwig Zuelzer (1870-1949) injected an extract called “*Acomatol*” into a dying diabetic patient who was in a coma. At first the patient showed improvement, but later suffered from side effects, and died when the Acomatol supply was exhausted (Zuelzer, 1908). Romanian physician Nicolae Constantin Paulescu (1869-1931) made a pancreatic extract “*pancreine*” that worked successfully in pancreatectomized dogs (Bliss, 1982).

The term insulin is derived from Latin word “*insula or island*”, and is given by Belgian physician Jean de Mayer (1878-1934) in 1909. In 1910, the first US medical doctor specialize in diabetes, Elliott Proctor Joslin (1869-1962), had founded a diabetic clinic, Joslin Diabetes Center, in Boston in the USA. He is rightly considered as the father figure of clinical diabetes (Gill, 1990; Joslin, 2005). Joslin advocated that diet and exercise are essential treatment of diabetes that is a hallmark, and this advice still remains an important component of diabetic management (Allan, 1972). He advised a prolonged fasting and of under-nutrition or under-nourishment as a cure for diabetes, as like the so-called “*starvation diet*” (Mazur, 2011).

In 1921, Canadian medical scientist, physician, and painter Frederick Grant Banting (1891-1941) and his assistant American-Canadian medical scientist Charles Herbert Best (1899-1978) have discovered insulin, which is used for the treatment of diabetes (Banting et al., 1922; Pyke, 1997).

They have isolated insulin from pancreatic islets and save lives of millions diabetes patients and have commenced a new era in diabetes treatment (von Engelhardt, 1989). Before the discovery of the insulin little

could be done for patients suffering from diabetes. Low calorie diets prolonged their lives but left them weak and near starvation (Karamanou et al., 2016).

9. Post-Insulin Period

In 1923, Eli Lilly and Company was producing enough insulin to treat ten thousand people with diabetes (Forsham, 1982). In 1925, home testing for sugar in urine through Benedict's solution was introduced. Benedict's solution is a reagent solution that contains cupric sulfate, sodium citrate, and sodium carbonate, and used to detect glucose in the urine. In 1926, American biochemist and pharmacologist John Jacob Abel (1857-1938) purified insulin, and isolated its crystalline structure. In 1927, an oral medication "horment" or "gluko horment" was developed as a replacement for insulin, but dropped out due to its side effects (Alam, 2017).

In 1935, Roger Hinshaw identified two types of diabetes, one being insulin sensitive (T1D), and the other insensitive (T2D) that open up new avenues of diabetes treatment (WHO, 2002). In 1942, M. J. Janbon discovered oral hypoglycemic agent sulfonylurea for the first time (Janbon et al., 1942). In 1955, the British biochemist Frederick Sanger (1918-2013) managed to fully sequence the bovine insulin and discovered its exact composition in terms of amino-acids (Vecchio et al., 2018). In 1980, the first human insulin was manufactured by American biochemist Graham Bell and his colleagues. Before this discovery, animal insulin, usually a purified form of porcine (pork) insulin was used (Alam, 2017).

Transplant pancreas in humans is the dream of physicians. In 1893, the first attempted has taken by the English doctor P. Watson Williams from Bristol to graft pancreatic tissue to cure diabetes. He has grafted three fragments of a pancreas obtained from a sheep into the subcutaneous tissue of a 15-year-old boy suffering from diabetes (Pybus, 1924). The first successful transplantation of pancreatic tissue was a whole organ pancreas transplant in 1966 carried out by the group of Kelly (Farney et al., 2016).

10. Conclusions

In this study we have tried to present a historical explanation of diabetes from ancient times. From the study we have observed that ancient Egyptians, Indians, Chinese, and Arabs have tried to describe the clinical signs and symptoms of diabetes mellitus. We have provided suffering of peoples for many centuries from this disease with very little existing treatment or relief. Now we have a lot of modern techniques and treatment methodologies; and many new developments are happening through the scientific research. After long-time scientific researches it is discovered that pancreas is the causative organ, and insulin is the tool of treatment of the diabetes.

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