

Diabetes Mellitus from Antiquity to Present Scenario and Contribution of Greco-Arab Physicians

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Summary

Diabetes is known since the age of antiquity. The first description that resembles the features of the disease is found in scroll of Ebers papyrus (1550 BC). Buqrat (460 BC), the father of Unani medicine did not specifically mentioned Diabetes in his writings, but there are accounts in the buqrat's writings that are consistent with the sign and symptoms of the disease. From the 9th to 11th Century AD, Arabic medicine was at its peak, during this period the Arab physicians translated the works of Greek physicians mainly Buqrat and Galenos and enriched them with the knowledge of that era. Ibn Sina a renowned physician of this era described the disease in his book *Al-Qanoon* and mentioned gangrene and collapse of sexual function as a complication of the disease. No progress was made till the 16th Century AD when Paracelsus reported that Diabetes was due to deposition of salt in the kidneys. After Paracelsus many scientist contribute their views to the development Diabetes, but scientific advances in the 19th and 20th centuries led to the discovery of insulin, which was the turning point in the management of diabetes mellitus. This led to an explosion of multidirectional research into the role of insulin in regulating metabolism and survival.

In the present paper historical aspect of Diabetes and contribution of Greco-Arab physicians will be discussed.

Key Words; Diabetes, Pancreas, Urine, Polyuria.

Diabetes is known since the age of antiquity, where symptoms of *Diabetes* were described. It is commonly believed that the history of medicine began with the Greeks, and before the time of **Buqrat (460 BC)**, Ancient Egypt (Misri) was the first civilization known to have an extensive study of medicine and to have left behind written records of its practices and procedures. It is proved by the discovery of the **Ebers papyrus** in the graves of Thebes by famous German Egyptologist **Georg Ebers** in 1862 AD. The *Ebers papyrus* is one of the most famous document relating to the ancient practice of medicine, written about 1550 BC. *Ebers papyrus* contains descriptions of various diseases including a polyuric state resembling *Diabetes Mellitus* (1,2,3). Although the Unani physician **Buqrat (460 BC)** "The father of medicine" did not specifically mentioned *Diabetes* in his writings, there are accounts in the *Buqrat's* writings that are consistent with the sign and symptoms of *Diabetes*, like excessive urinary flow with wasting of the body

(3). **Arataeus** and **Jalinoos (Galen)** were followers of *Buqrat*. **Arataeus (81-138 AD)** provided the first accurate description of the symptoms of *Diabetes*. He was the first who use the term "*Diabetes*" in connection with this ailment, which means "to run through" or "Siphon". He described the disease as "*Diabetes* is a dreadful affliction, not very frequently among men, being a melting down of the flesh and limbs into urine" (2, 4,5,6,7). **Jalinoos (131-201 AD)**, a contemporary of *Arsyatoos*, the most influential medical writer of all time, discussed *Diabetes* in a number of his books. He described the condition as rare, as he had only seen two cases, he referred to the ailment as "Diarrhoea Urinosa (Diarrhoea of urine)" ,and "dipsakos (the thirsty disease)"(2,3,8). However, the association of polyuria with a sweet tasting substance in the urine was first reported in Sanskrit literature dating from the 5th - 6th century AD at the time of **Susruta, Charaka and Vagbata** with the name of "*Madhumeha*". They described the urine of polyuric patients

as having the taste like honey, being sticky to touch and strongly attracting the ants. The Indian description of that time also contains *Diabetes* like conditions of two types: congenital and late onset. They also described the relation of *Diabetes* to heredity, obesity, sedentary life and diet. During the same era, Chinese and Japanese physicians also described *Diabetes* and the sweetness of urine of *Diabetes* patients, which apparently attracted dogs. They also observed that people with *Diabetes* were prone to develop boils and an affliction which clinically resembles tuberculosis (2,3,9). During the 9th -11th centuries AD, Arabic medicine was at its peak of achievements and Arabian physicians translated the works of *Buqrat* and *Jalinoos* and enriched them with latest knowledge of that era. Two prominent physicians of this era who contributed to the knowledge of *Diabetes* (*Ziabetus*) were **Shaikh-Ul-Rais Bu Ali Ibne Sina (960-1037 AD)** and **Musa Bin Maimoon (1135 AD)**. *Ibne Sina* described accurately the clinical features of the disease and mentioned two specific complications of the disease, namely gangrene and the collapse of sexual function. While on the other hand *Musa Bin Maimoon* claimed to have seen more than 20 cases. He proposed that *Diabetes* was caused by the sweet water of river Nile and the prevailing heat that spreads over the kidneys (2,3). No further progress was made in the understanding of *Diabetes* until the 16th century AD. When the Swiss physician **Von Hohenheim (Paracelsus)** reported that urine of Diabetic patients contained an abnormal substance which remained as a white powder after evaporation, he concluded that this substance was salt and that *Diabetes* was due to the deposition of salt in the kidneys causing thirst of the kidney and polyuria (2). The modern history of *Diabetes* began with the **Thomas Willis's (1621-1675 AD)** observations of *Diabetes* in 1674 AD and **Matthew Dobson's** experiments in 1776 AD that conclusively established the diagnosis of *Diabetes* in the presence of sugar in the urine and blood. *Diabetes* was no longer considered a rare ailment. *Thomas Willis* referred to *Diabetes* as the "Pissing evil" and noted that in patients with *Diabetes*, "The urine was wonderfully sweet, as if it were imbued with honey or sugar". He claimed that *Diabetes* was primarily a disease of the blood and not the kidneys. *Willis* proposed that the sweetness first appeared in the blood

and was later found in the urine. During the same era **Thomas Sydenham (1624-1689 AD)** speculated that *Diabetes* was a systemic disease arising in the blood where "*Chyle*" was incompletely digested and its non-absorbed residue had to be excreted. After **Thomas Sydenham, Johann Conrada Brunner (1653-1727 AD)** came very close to discovering pancreatic *Diabetes* when he observed in 1682 AD that, After the incomplete removal of the pancreas from a dog, ".....the animal made water very frequently and that he was very thirsty, drinking largely of water in proportion to the discharge of urine" (2,3,10,11,12, 13,14). **Cullen** was the first person who distinguished *Diabetes* into two types. In this classification, we find first time a distinction between *Diabetes*, with the urine of "the smell; colour and flavor of honey," and *Diabetes*, with limpid but not sweet urine (3). The concept of *Thomas Sydenham* was further elaborated by **Matthew Dobson (1735-1784 AD)**, who provided experimental evidence that people with *Diabetes* pass sugar in their urine. He gently heated two quarts of urine to dryness. The remaining residue was a whitish cake, which *Dobson* wrote "was granulated and broke easily between the fingers; it smelled sweet like brown sugar, neither could it be distinguished from sugar, except that the sweetness left a slight sense of coolness on the palate". Moreover he concluded that this substance had previously existed in the serum rather than being formed in the kidneys. He wrote "this idea of the disease explains its emaciating effects from so large a proportion of the alimentary matter being drawn off by the kidneys, before it is perfectly assimilated and applied to the purpose of nutrition (15). In 1788 AD **Thomas Cawley** described that *Diabetes* may follow damage to the pancreas, such as through calculus formation (16). Twenty years after the *Matthew Dobson*, in 1797 AD **Matthew Baillie** stated that "upon examination of the kidneys.....it seemed probable that *Diabetes* depends, in a considerable degree, upon a deranged action of the secretory structure of the kidneys, by which the blood there is disposed to new combinations" the effect of which is the production of "a saccharine matter". He also proposed that "the chyle may be so imperfectly formed, as to make the blood be more readily changed into a saccharine matter, by the action of the kidneys" (17). In 1798 AD, a year after the

Matthew Baillie, "**John Rollo**" a surgeon, expressed his opinion that "the Diabetes Mellitus" is a disease of the stomach and its immediate cause is a morbid condition of stomach evolving from vegetable substances containing saccharine matter, which is quickly separated as a foreign body by the kidney" (18). Further he was the first who use the adjective "*Mellitus*" to distinguish the condition from other polyuric diseases in which glycosuria was absent and urine was tasteless. *Rollo* made other contributions to the study of Diabetes, including descriptions of "cataract due to Diabetes" and odour of acetone on the breath of some Diabetes patients (19). In 1815 AD, *Michel Eugene Chevreul (1786-1889 AD)* published his experimental findings on urine and stated that sweet substance found in urine of Diabetes patients was to be identical to grape sugar (20). In 1839 AD, *John Elliotson* speaks about "grief", "chills" and, "excess of venery" as possible etiological factors for Diabetes in his "Principles and practice of medicine" (21). In the first half of the 19th century *Claude Bernard (1813-1878 AD)* discovered that the liver releases a substance that affects blood sugar levels. In 1875 AD, he isolated a starch like substance that he called "Glycogen", which was the precursor of glucose, "the internal secretion" of the liver. This observation established the liver's role as a vital organ in Diabetes. He also demonstrated that the central nervous system was involved in controlling the blood glucose concentration. He also performed many systematic experiments on the pancreas (3,22, 23, 24). During mid 19th century AD, *William Prout (1785-1859 AD)* described "exposure to cold", "attacks of rheumatism and gout", "The drinking of cold fluids while heated", and "mental anxiety and distress" as the most frequent exciting causes of Diabetes. He was the first, who recognized the coma as a complication of Diabetes (25). Further in 1869 AD, *H.D. Noyes*, observed that a form of "retinitis" developed in glycosuric patients (2), during the same year, *Paul Langrhan (1847-1888 AD)* had noticed small clusters of ductless cells in teased preparations of pancreas, he simply described these structures without speculating as to their possible function. It was only in 1893 AD that *Edouard Laguesse (1861-1927 AD)* suggested that these clumps of cells, which he named the "*islets of langerhans*" in honour of langerhans and suggested

that they might constitute the endocrine tissue of the pancreas (2,3,26,27). In 1874 AD, *Prof. A. Kussmaul (1822-1902 AD)* described the "*air hunger*" of ketoacidosis (28). In 1875 AD, *Dickinson* published a paper "Diabetes, in his diseases of the kidneys", in which he defined Diabetes as "a disease of the nervous system characterized by the secretion of saccharine containing urine" (29). In 1877 AD, *Etienne Lancereaux (1829-1910 AD)* demonstrated a causal relationship between Diabetes and lesions of the pancreas (30), and his friend, *Apollinaire Bauchardat (1806-1886 AD)*, began the modern therapy of Diabetes by limiting carbohydrates in the diet, advocating fast days, and using exercise to help control glycosuria (31). In 1889 AD, *Oskar Minkowski (1858-1931 AD)* and *Josef Von Mering (1849-1908 AD)* demonstrated conclusively that removal of the pancreas from a dog results in the development of fatal Diabetes. This observation firmly established the role of the pancreatic disorders in causing Diabetes (32,33,34). Further in 1901 AD, *Eugene Undsay Opie's (1873-1962 AD)* pathologic study on Diabetes Mellitus established that Diabetes is caused by a lesion of the pancreas, and the lesion is of such kind in which the islands of langerhans are destroyed or injured (35). In 1908 AD, *Georg L. Zuelzer (1870-1949 AD)* and *Nicolas Paulesco (1869-1931 AD)* had prepared potent pancreatic extract before 1921 AD (36). In 1909 AD, *Jean De Meyer* gave the name "*insulin*" derived from the latin word *insula* (insula= island), to the glucose lowering hormone, whose existence at that time was still hypothetical, which he postulated was produced by the islet tissue (37). *Further Moses Barron (1883 AD)* give conclusion regarding the relationship of islets of langerhans to Diabetes "...that the islets secrete a hormone directly into the lymph or blood streams (*Internal secretion*), which has a controlling power over carbohydrate metabolism" (38). The finding of *Moses Barron* triggered the investigations of *Frederick Grant Banting (1891-1941 AD)* and *Charles Herbert Best (1899 AD)*. In December 1921 AD, they got success in isolation of insulin and published the results of their research on "The internal secretion of the pancreas" in which they were able to demonstrate the reversal of the metabolic changes of Diabetes by injection of a potent extract of the pancreatic islands

(39,40,41). On 11th Jan 1922 AD, the first patient of Diabetes a 14 year old boy named **Leonard Thombson** was treated with insulin (11,42). In 1923 AD Eli Lilly begins commercial production of insulin, and called it "Isletin Insulin." In 1925 AD Home testing for sugar in the urine through Benedict's solution was introduced. In 1927 AD an oral medication called "horment" or "glukohorment" was developed as a replacement for insulin, but side effects are unacceptable and very soon dropped out. In 1930s AD Insulin was further refined to Protamine zinc insulin, a long-acting insulin that provide more flexibility. In 1936 AD **Himsworth** divided Diabetics into two types based on "insulin sensitivity." In 1940's AD neutral protamine Hagedorn insulin was introduced and the connection was established between Diabetes and long-term complications of kidney and eye diseases. In late 1940's AD **Helen** Free developed the "dip-and-read" urine test (Clinistix) allowing instant monitoring of blood glucose levels. In 1951 AD **Lawrence** and **Bornstein** measured the amount of insulin in the blood and noted that older and obese patients with Diabetes have insulin, but those who were young have none. In 1955 AD Oral drugs that help lower blood glucose levels was introduced. In 1959 AD, Two major types of diabetes are recognized: Type 1 (Insulin-Dependent) Diabetes and Type 2 (Non-Insulin-Dependent) Diabetes. During the 1959-1960 AD **Yellow** and **Berson** developed the radioimmunological assay (RIA) procedure, to measure insulin with much greater precision than earlier techniques, for that **Yellow** received the Nobel prize in 1977 AD. In 1964 AD, The first strips for testing blood glucose were used. In 1970 AD, First blood glucose meter (Ames) and Insulin pumps were introduced. During the same year Laser therapy was used to slow down or prevent blindness due to Diabetes. In 1973 AD, U-100 insulin is introduced. In 1976 AD, the glycosylated hemoglobin (A1C) test was introduced as a monitor of glycaemic control. The manufacturing of insulin changed dramatically with the advent of DNA technology that allows synthesis of a genetically engineered "human" type of insulin, and in 1978 AD, Production of the first recombinant DNA insulin was announced. In 1979 AD, Type 1 and Type 2 Diabetes are formally recognized by the American Diabetes Association. Type 1 is also called Insulin

Dependent Diabetes Mellitus (IDDM), and Type 2 is called Non Insulin Dependent Diabetes Mellitus (NIDDM). In 1983 AD, the first biosynthetic human insulin, and "Reflolux", later known as "Accu-Chek" (allows blood glucose self-monitoring) was introduced. In 1996 AD, the FDA approved the first recombinant DNA human insulin analogue, lispro (Humalog). In 2001 AD, FDA approved Cygnus' first-generation model of the GlucoWatch Biographer for use by adults - the first frequent, automatic and non-invasive glucose monitor. In 2003 AD, the names Insulin Dependent Diabetes Mellitus (IDDM) for Type 1 and Non Insulin Dependent Diabetes Mellitus (NIDDM) for Type 2 diabetes are formally dropped. Today Researchers are working on an insulin patch and inhaled insulin, Genetic engineering is being used to manipulate cells so they secrete insulin. A sensor-computer-pump system that mimics the insulin response of the normal pancreas is being developed to function as an "artificial pancreas". Apart from these, various researches are still going on, to explore new aspects of Diabetes and its management. (43, 44, 45, 46, 47, 48, 49, 50)

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