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Review Article

The Historical Evaluation of Diabetes Mellitus: A short review

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Abstract

Introduction-History serves as the foundation for research and development, as well as a source for generating hypotheses. Diabetes is one of the oldest known diseases, dating back to ancient times. The ancient Egyptians described clinical features similar to diabetes mellitus 3500 years ago. The first description resembling the disease's features is found in Ebers's papyrus (1550 BC). Zakariyyā Rāzī, notes that diabetes patients often experience intense thirst, but the ingested water is simply excreted without absorption. In Unani Medicine, Diabetes is described under the caption of Amraz-e-Gurda. **Objective-** This article reviews the historical context of diabetes, from its ancient roots to modern advancements in insulin therapy, including needle-free alternatives like inhaled and oral insulins. **Methodology-** The methodology for this review involves an in-depth examination of foundational texts from the Unani system of medicine, along with a comprehensive review of relevant academic literature and published research. **Conclusion-** This article explores the historical origins of diabetes mellitus, a major global health challenge despite being largely preventable. From ancient documentation to the discovery of insulin, the journey of understanding and treatment has been transformative. Advances in insulin forms and delivery have improved patient outcomes, though it remains a treatment, not a cure. The discovery of insulin is a story of perseverance and scientific breakthroughs, inspiring future research in pharmacology. This historical journey underscores diabetes' profound impact on medical science and human health.

Keywords: Diabetes Mellitus, *Dhayābītus*, Historical background, Unani Medicine

INTRODUCTION:

Diabetes Mellitus poses a major challenge to 21st century healthcare. Despite being a chronic, non-communicable disease (NCD) that is largely preventable, it remains a leading cause of millions of deaths annually. It contributes to a range of severe, life-threatening complications[14]. According to the World Health Organization (WHO), approximately 346 million people worldwide are affected by diabetes, with India and China accounting for the largest share of the global diabetic population. The World Health Organization (WHO) highlights a significant rise in the global prevalence of diabetes among adults, with numbers expected to grow from 135 million in 1995 to 300 million by 2025. This increasing trend is attributed to factors such as population aging, urbanization, dietary changes, decreased physical activity, and other unhealthy lifestyle and behavioral patterns [15]. The WHO defines diabetes mellitus (DM) as a diverse metabolic disorder marked by persistent hyperglycemia and disruptions in carbohydrate, fat, and protein metabolism [13]. The term diabetes was first coined by Aretaeus of Cappadocia (81-138 AD). The term Diabetes originates from the Greek word Diabainein or Diabainmo, meaning to pass through, run through, or siphon. The word Mellitus, derived from Latin, translates to sweetened with honey. In the Unani system of medicine, diabetes mellitus is referred to as *Dhayābītus Shakri*. Classical Unani texts refer to diabetes using various terms, including *Dhayābīṭus, Ziasaqus, Qaramees, Dawwāriyya, Dūlābiya, Zalqul Kulya, Istisqā-e-Anmas, Dipsakos, Mu'attisha, A'atisha, and Parkāriyya.*

According to the majority of Unani practitioners *Dhayābītus Shakri* is characterized by excessive thirst, excessive urination, presence of sugar in the urine, increased appetite, gradual loss of body weight, and complications, such as diabetic gangrene and sexual dysfunction, described in detail [8].

In Unani classical texts, various terms for diabetes are cited by different scholars. For instance, Rāzī referred to it as *Dhayābīṭus* in *Al Ḥāwī* [16]. Ibn-Sīnā used terms like *Dawwāriyya*, *Dūlābiya*, *Zalq al Kulya*, and *Zalq al Majārī*. Additional names mentioned in *Al-Qānūn fi'l Ṭibb* include *Ziasqomas* and *Qramees* [8]. Additional terms for diabetes mentioned in various texts include "Illat Parkāriyya," as noted in *Kitāb al-Taysīr* [20]. *Salas al-Bawl* and *Istisqā'* -e-*Anmas* in *Ṭibb-i-Akbar* [17]. *Mu'aṭṭ isha, Bawl Shīrīn ,Madhumeha,* and *shahdiya* in *Iksīr-i-A'ẓam [18,19]*.

Historical Background of *Dhayābītus*

Diabetes Mellitus is a disease recognized since ancient times, its history is categorized into three separate eras: the ancient era, the diagnostic era, and the experimental eras, culminating in the discovery of insulin.

Ancient Era:

Around 3500 years ago, ancient Egyptians documented clinical symptoms resembling diabetes mellitus. Georg Ebers's discovery of the Ebers Papyrus (Fig 1) in the graves of Thebes in 1873 revealed detailed accounts of diseases, including a condition characterized by excessive urination similar to diabetes mellitus, written around 1550 BC [6,1,2,5].

Fig 1: Ebers Papyrus (Source: Wikipedia)

Aretaeus of Cappadocia (Fig 2) first introduced the term 'diabetes during the 2nd century AD (81-138 AD). He characterized diabetes as a stomach disorder [2,11].

Fig 2: Greek physician Aretaeus of Cappadocia (81-138 AD) Source: Wikipedia

Aulus Cornelius Celsus (30 BC-50 AD) initially outlined the clinical aspects of diabetes. Still, it was Arataeus of Cappadocia (second century AD) who offered a comprehensive description and coined the term "Diabetes" from the Greek word for "siphon." Arataeus noted that the disease leads to a shortened lifespan due to the loss of muscle mass, which is excreted in the urine [3,4].

Galen, (Fig 3) the esteemed Roman physician (129-199 AD), rejected Aretaeus' theory, attributing diabetes to a kidney disorder. He used alternative terms such as "diarrhea urinosa" and "dipsakos," highlighting the prominent symptoms of polydipsia and excessive thirst. Galen perceived diabetes as a rare ailment, encountering only two cases in his lifetime [7,6,2].

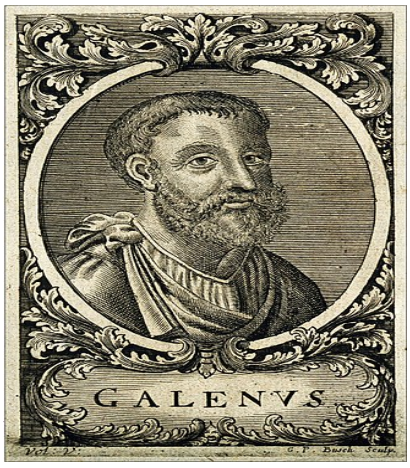

Fig 3: Roman physician Galen (129-199 AD) Source: Wikipedia

Hippocrates, also known as Buqrāṭ (460 BC), "The father of medicine" (Fig 4) documented a condition characterized by excessive urination and body wasting [6].

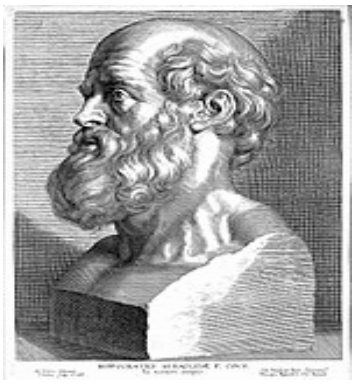

Fig 4: Buqrāṭ (460 BC) Source: Wikipedia

Ancient healers noticed during this time that ants tended to be drawn to the urine of people who had this disease [11]. Sushruta and Charaka (Fig 5) renowned Indian physicians from the 5th and 6th centuries AD, initially noted the sweetness of diabetic urine resembling honey and named it "Madhumeha" (honey urine). They delineated two distinct types of diabetes: one afflicting older and overweight individuals, and another targeting asthenic individuals who had shorter life expectancies [2].

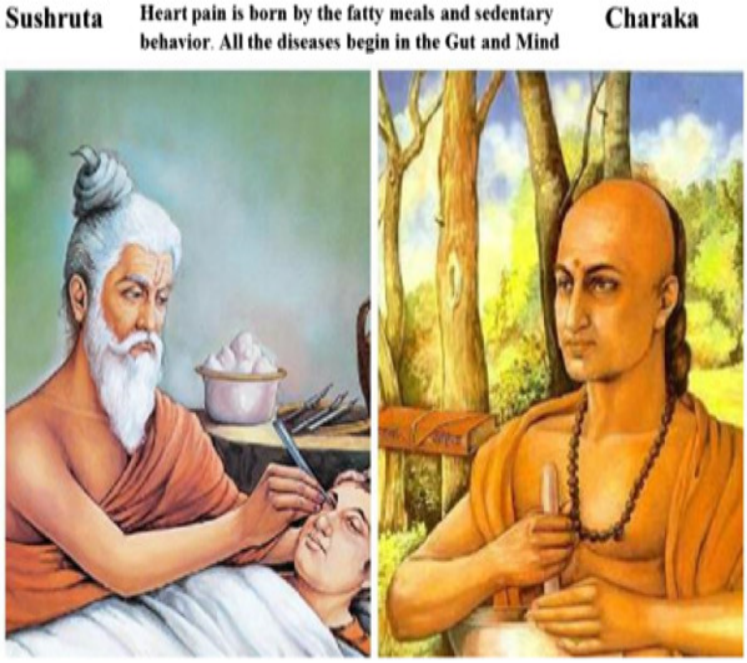

Fig 5: Sushruta and Charaka (5th and 6th centuries AD)

In the same period, Chinese and Japanese doctors also referenced diabetes along with

sweet-tasting substances for testing [1]. During the medieval period, numerous Unani physicians documented diabetes, notably, Ibn Sīnā (980-1037 AD) provided a precise portrayal of the clinical manifestations of diabetes mellitus [1,2].

Fig 6: Ibn Sīnā (980-1037 AD)

Ibn Sina (Fig 6) authored an extensive medical text, *Al-Qanun fi al-Tibb*, which provided a comprehensive account of diabetes. Ibn Sina termed the disease *Dūlābiya* (water wheel) and *Zalqul Kulya* (diarrhea of the kidneys). He described its clinical characteristics, such as sweet-tasting urine and heightened appetite, along with complications like diabetic gangrene and sexual dysfunction. Notably, Ibn Sina was the first to distinguish diabetes-related emaciation from other causes of excessive urination. [8]

Diagnostic Era

During the 16th century and onward, Diabetes Mellitus was identified as a distinct disease. Progress in understanding this condition primarily occurred in Europe during this time, with little notable input from Unani physicians, indicating a stagnation in medical advancements. Paracelsus (1493-1541 AD), in the 16th century, disregarded ancient theories and proposed that diabetes stemmed from an imbalance in sulphur and electrolytes in the blood, leading to salt deposition in the kidneys, inflammation, and subsequent polyuria [1,9]. During the 17th century, Thomas Willis (1621-1675 AD) (Fig 7) noted the sweet taste of diabetic urine, while Thomas Sydenham (1624-1689 AD) (Fig 8) hypothesized that diabetes originated as a systemic ailment rooted in the blood, where incompletely digested "chyle" was expelled in urine.

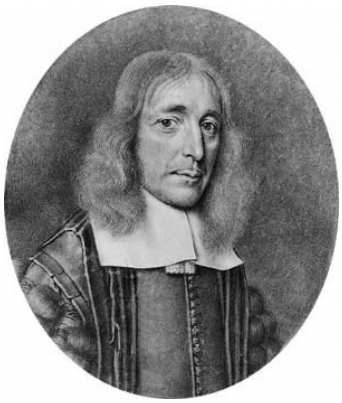

Fig 7: Thomas Willis (1621-1675 AD) Source: Wikipedia

Fig 8: Thomas Sydenham (1624-1689 AD)

In the 18th century, Mathew Dobson (1745-1784 AD) demonstrated the presence of a sugary substance in the serum and urine of diabetic patients, suggesting its pre-existence in the serum rather than its formation in the kidneys. This pivotal discovery marked the initial understanding of diabetes as a systemic disorder. Further observations revealed that not all diabetic patients exhibited this sweet substance in their urine, leading to the recognition of two fundamental types of diabetes [2]:

1. **Diabetes Mellitus**
2. Diabetes Insipidus

John Rollo coined the term "Mellitus," meaning honey, to differentiate it from other polyuric conditions. He also documented diabetic cataracts and the scent of acetone. Thomas Cowley (1788 AD) was the first to examine the connection between diabetes and the pancreas. In 1788, Thomas Cawley proposed that

diabetes might stem from pancreatic damage, providing crucial insights into the contemporary pathology of the disease [2].

In 1815, Eugene Chevreul in Paris demonstrated that glucose was the sugar present in the urine of individuals with diabetes. In 1848, Von Fehling introduced a quantitative test to measure glucose in urine [12].

Experimental Era

The mid-19th century marked a significant period during which the pancreatic role in regulating glucose became evident, and the biochemical abnormalities of diabetes were first elucidated. This era was pivotal for various medical disciplines. Claude Bernard (1813-1878 AD), (Fig 9) a renowned physiologist, observed the storage of sugar in the liver as glycogen and demonstrated the involvement of the central nervous system in blood glucose control. In 1869, Paul Langerhans (1847-1888 AD), (Fig 10) identified small cell clusters within the pancreas, later named "islets of Langerhans" by Edward Laguesse in 1893, who suggested their potential endocrine function [2]. In 1889, Oskar Minkowski (1858-1931 AD) and Josef Von Mering (1849-1908 AD) conducted experiments demonstrating the pancreas's ability to lower blood sugar levels. They achieved this by surgically removing the pancreas from dogs, resulting in a hyperglycaemic state [2].

Fig 9: Claude Bernard (1813-1878 AD) Source: Wikipedia

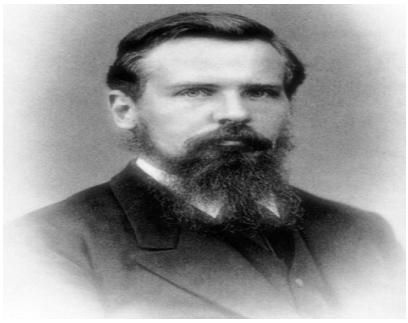

Fig 10: Paul Langerhans (1847-1888 AD)

During the 20th century, Jean De Meyer coined the term "insulin" for the secretion of the Islets of Langerhans, in 1909, derived from the Latin word for "island." Then, in 1921, Frederic G. Banting (1891-1941 AD), (Fig 11) and Charles Best (Fig 12) confirmed that insulin played a crucial role in carbohydrate metabolism [2,10]. In January 1922, Leonard Thompson, a 14-year-old boy dying from diabetes in a Toronto hospital, became the first person to receive an injection of insulin. Within 24 hours, Leonard's dangerously high blood glucose levels dropped to near-normal levels. In 1936, Herold Percival Himsworth distinguished between type 1 and type 2 diabetes. Insulin from cattle and pigs was used for many years to treat diabetes and saved millions of lives, but it wasn't perfect, as it caused allergic reactions in many patients. Later, in 1977, Herbert Boyer successfully genetically engineered synthetic human insulin [12]. In the 1980s and 1990s, analog insulins were developed as genetically engineered versions of insulin with modified amino acid sequences designed to improve absorption, distribution, metabolism, and excretion. In 1996, Eli Lilly launched the first analog insulin, lispro, under the brand name Humalog. Following this, aspart was approved and released in 2000, and glulisine came out in 2004 [21].

Fig 11: Frederick Grant Banting (Source: Wikipedia)

Fig 12: Charles Best (Source: Wikipedia)

In the 21st century Regarding needle-free insulins, Exubera, the first inhaled insulin, was developed by Sanofi-Aventis and Pfizer and marketed by Pfizer in 2006. The concept of delivering insulin via inhalation as an aerosol was first proposed in 1925 and revisited in 1971. Pfizer, in collaboration with Nektar, conducted research on aerosolized formulations, leading to the creation of a dry powder with suitable particulate properties for alveolar deposition. While Inhaled insulin has low bioavailability (about 9% of the amount inhaled) but results in adequate serum insulin levels, therefore being as effective as subcutaneously administered insulin at controlling glucose levels in both type 1 and type 2 diabetes. However, in October 2007, Pfizer decided to discontinue the product. Another promising product is buccal/oral insulin. Oralin, approved in 2005 in Ecuador and marketed by Generex, utilizes RapidMist technology to deliver a combination of insulin, surfactants, and lipids to the buccal mucosa [21].

Insulin is now available in various forms, ranging from regular human insulin, which mimics the body's natural production, to ultra-rapid and ultra-long-acting options. Decades of research have provided people with diabetes a wide array of formulations and delivery methods tailored to their individual needs and lifestyles. From products like Humalog and Novolog to devices such as insulin pens and pumps, insulin has significantly advanced over time. While it isn't a cure for diabetes, it is undeniably a life-saving treatment.

Methodology

The foundational and traditional texts of the Unani system of medicine were thoroughly examined, and the literature and resources referenced in this review article were derived from those sources. Information was gathered from databases including published research articles, journals, PubMed, Google Scholar, and ScienceDirect.

Conclusion

This research article offers an in-depth examination of the historical origins of Diabetes Mellitus. Diabetes Mellitus continues to present a formidable challenge to global healthcare, with millions of individuals affected and a growing prevalence worldwide. Despite being largely preventable, its complications lead to significant morbidity and mortality. The historical journey of understanding and treating diabetes, from ancient documentation to the discovery of insulin, has been a long and transformative one. Advancements in treatment, including the development of various insulin forms and delivery methods, have dramatically improved the quality of life for those affected. While insulin is not a cure, its life-saving role remains indispensable, offering hope for better management and control of diabetes, even as the medical community strives toward further advancements in care and prevention. The history of insulin's discovery is a compelling tale of dedication, perseverance,

hard work, unravelling complex scientific puzzles, and overcoming professional challenges. It serves as an inspiration for future researchers in drug discovery and various areas of pharmacology. This journey from ancient observations to modern therapeutic breakthroughs highlights the enduring quest for understanding and treating diabetes, underscoring its profound impact on medical science and human health.

Summary of Historical Background

Summary of Historical Background

Periods	Sources	Observations
15th century BC	Ebers Papyrus (Egypt)	Clinical description of a polyuric condition resembling diabetes mellitus
5th & 6th century AD	Sushruta and Charaka	Clinical description including sugary urine, obese and thin patients distinguished.
10th century AD	Avicenna	Clinical descriptions including sugary urine, gangrene, and impotence
17th century AD	Thomas Willis England	Diabetic urine contains sugar
18th century AD	Mathew Dobsen (England) Thomas Cawley (England)	Diabetic serum contains sugar, Diabetes may follow pancreatic damage.
19th century AD	Claude Bernard (France) Paul Langerhans (Germany)	Glucose stored as hepatic glycogen, ligation of pancreatic duct causes exocrine degeneration Identified pancreatic islets pancreatectomy causes diabetes
20th century AD	Jean de Meyer (Belgium) George Zulzer (Germany) Nicholas Paulesco (Romaia) Israel Kleiner (USA)	Hypothetical pancreatic glucose-lowering hormone named insulin Isolated hypoglycaemic extract from the pancreas
21st century	Sanofi-Aventis	Approval of Exubera, the first inhaled insulin

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Conflicts of interest
The author declares no conflicts of interest.

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