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## MINIREVIEWS



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MINIREVIEWS

# Milestones in the history of diabetes mellitus: The main contributors

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## Abstract

Diabetes mellitus is a group of metabolic diseases involving carbohydrate, lipid, and protein metabolism. It is characterized by persistent hyperglycemia which results from defects in insulin secretion, or action or both. Diabetes mellitus has been known since antiquity. Descriptions have been found in the Egyptian papyri, in ancient Indian and Chinese medical literature, as well as, in the work of ancient Greek and Arab physicians. In the 2nd century AD Aretaeus of Cappadocia provided the first accurate description of diabetes, coining the term diabetes, while in 17th century Thomas Willis added the term mellitus to the disease, in an attempt to describe the extremely sweet taste of the urine. The important work of the 19th century French physiologist Claude Bernard, on the glycogenic action of the liver, paved the way for further progress in the study of the disease. In 1889, Oskar Minkowski and Joseph von Mering performed their famous experiment of removing the pancreas from a dog and producing severe and fatal diabetes. In 1921, Frederick Banting and Charles Best extended Minkowski's and Mering's experiment. They isolated insulin from pancreatic islets and administrated to patients suffering from type 1 diabetes, saving thus the lives of millions and inaugurating a new era in diabetes treatment.

**Key words:** History of endocrinology; Metabolic disorder; Diabetes mellitus; Aretaeus of Cappadocia; Insulin



**Core tip:** Diabetes mellitus has been known since antiquity and despite therapeutic advances it still remains an incurable chronic disease. In our historical article, we attempt to provide the most important steps in the history of diabetes mellitus from antiquity till nowadays. The contribution of leading medical figures

such as Aretaeus of Cappadocia, Thomas Willis, Claude Bernard, Oskar Minkowski, Joseph von Mering, Frederick Banting and Charles Best is mentioned, in an attempt to highlight the development of our current knowledge in diabetes mellitus.

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## INTRODUCTION

Diabetes mellitus is a group of metabolic diseases involving carbohydrate, lipid, and protein metabolism. It is characterized by persistent hyperglycemia, as a result of defects in insulin secretion, insulin action or a combination of both, defective secretion and incorrect action. There are two main types of diabetes mellitus: Type 1 (insulin-dependent), and type 2 (non-insulin-dependent). Type 1 diabetes results by the autoimmune destruction of the β-cells of the pancreatic islets and type 2 diabetes is caused from impaired insulin secretion and resistance to the action of insulin[1]. Current epidemiological data reveal that 9% of adults, 18 years of age and older, has diabetes mellitus while it was estimated that in 2012, 1.5 million people died due to the disease. According to the World Health Organization, diabetes will be the 7th leading cause of death in 2030[2-4].

The disease has a long history reaching back into antiquity. However, during that period, due to a poor knowledge of anatomy, pathophysiology and lack of diagnostic tools, the disease remained extremely perplexing to physicians.

Nevertheless, physicians in antiquity observed the distinctive features of diabetes and proposed several therapeutic approaches. In Ebers papyrus, dated back to 1500 BC, we may find passages describing patients who suffer from excessive thirst, copious urination and they are treated by plants' extracts. However, according to the Egyptian endocrinologist, historian of medicine and translator of the Ebers papyrus Paul Ghalioungui (1908-1987), the description of a probable diabetes, in Ebers, is regarded as unsatisfactory and probably wrong. In Kahun papyrus (c. 2000 BC) there is just the title of a recipe for the "Treatment of a thirsty woman", but the text is missing[5]. So, we may assume that ancient Egyptians could not recognize behind the symptoms of specific disease entity such as diabetes.

Around the 5th century BC, the famous Indian surgeon Sushruta, in his work Samhita, identified diabetes, by using the term madhumeha (honey-like urine) and pointed out not only the sweet taste of the urine but also its sticky feeling to the touch and its ability to attract the ants (!). Sushruta further mention that diabetes affects primarily the rich castes and is related to the excessive food consumption as the rice, cereals and sweets[6].

In ancient China, Chang Chung-Ching (ca. 160-ca. 219), referred to as "the Chinese Hippocrates", described polyuria, polydipsia and loss of weight as symptoms of a specific disease, while in 7th century AD Chen Chuan recorded the sweet urine in diabetes mellitus and named the disease Hsiao kho ping mentioning its characteristic symptoms: intense thirst, copious drinking and large amounts of urine which is tasted sweet. In an attempt to treat that disease his colleague Li Hsuan proposed the abstinence from wine, salt and sex[6].

From the 8th century onwards, physicians observed the tendency of diabetic patients to develop skin infections as furuncles, rodent ulcers and troubles of the eyesight. In 11th century AD, the celebrated Arabo-islamic physician Avicenna (980-1037) in his textbook El-Kanun (Canon of Medicine) described diabetes and mentioned gangrene and sexual dysfunction as its complication. Years later, the medieval scholar Moises Maimonides (1138-1204) described in detail diabetes, including the symptoms of acidosis[6].

Ancient Egyptians, Indians, Chinese and Arabs tried to describe the clinical signs and symptoms of diabetes mellitus. However, few are the main protagonists in the history of diabetes mellitus who contributed significantly, not only to its diagnosis and treatment but also to the development of our current notions on the disease, paving the way for further study and establishing a new medical sub specialty, diabetology.

## ARETAEUS OF CAPPADOCIA (2nd CENTURY AD) AND THE FIRST ACCURATE DESCRIPTION OF DIABETES

Aretaeus, surnamed the Cappadocian, is probably the greatest physician of the Greco-Roman antiquity after Hippocrates, and at least equal of Galen. He was born in Cappadocia, a region in eastern Asia Minor, studied medicine in Alexandria and practiced in Rome probably during the 2nd century AD. Areataeus' medical practice was based on the principals of the Pneumatic school believing not only in the vital role of pneuma (air) but embracing also the theory of the four humors (heat, coldness, moisture, dryness). In his two treatises, De causis et signis morborum acutorum et diuturnorum (on the causes and symptoms of acute and chronic diseases) and De curatione morborum acutorum et diuturnorum (on the cure of acute and chronic diseases), written in Ionic dialect, Aretaeus impresses us by the vividness and the simplicity of his descriptions. Among others he described, in an accurate way for his time, leprosy, asthma, pneumonia cancer, tetanus, hysteria, epilepsy, gout[7,8] (Figure 1).

Before Aretaeus, ancient Greek medical authors such as Rufus of Ephesus (c. 1st century AD) and


**Figure 1 The distinguished physician Aretaeus of Cappadocia.** (Source: Wellcome Library, London).

Galen (130-c.201) were mentioning that diabetes was provoking excessive thirst, polyuria, emaciation of the human body, leading sometimes to death. The symptom of polyuria gives the idea to Galen, who according to his own writings he has seen the disease only twice, to name diabetes diarrhea urinoma (diarrhea of the urine). Later, the term diabetes was introduced into medical nomenclature by Aretaeus. It arises from the Greek verb διαβαινω (diabaino) which means I pass through and diabetes, the condition that the fluid runs through.

In the following passage of Areateus' work, we may admire the clinical presentation and interpretation of diabetes: "Diabetes is a wonderful affection, not very frequent among men… The course is the common one, namely, the kidneys and the bladder; for the patients never stop making water, but the flow is incessant, …. The nature of the disease, then, is chronic, and it takes a long period to form; but the patient is short-lived, if the constitution of the disease be completely established; for the melting is rapid, the death speedy. Moreover, life is disgusting and painful; thirst; excessive drinking, which, however, is disproportionate to the large quantity of urine, for more urine is passed; and one cannot stop them either from drinking or making water. Or if for a time they abstain from drinking, their mouth becomes parched and their body dry; they are affected with nausea, restlessness, and a burning thirst; and at no distant term they expire. Thirst, as if scorched up with fire... But if it increase still more, the heat is small indeed, but pungent, and seated in the intestines; the abdomen shriveled, veins protuberant, general emaciation, when the quantity of urine and the thirst have already increased; and when, at the same time, the sensation appears at the extremity of the member, the patients immediately make water". For the treatment of the disease he proposes the consumption of cereals, milk and wine, the topical application of cataplasms and the administration of Theriac, the famous cure all remedy of antiquity[7,8].

However, it remains unknown how Aretaeus made such a precise description of a relatively rare disease during that period, just by observation.

## THOMAS WILLIS (1621-1675) AND THE TERM "MELLITUS"

The English anatomist and physician Thomas Willis, is considered one of the greatest physicians in 17th century. He lived in a period that England was in political and religious turmoil and he needed to interrupt several times his studies. Willis studied classics and then medicine at Oxford where he was appointed Professor of Natural Philosophy to the highly prestigious Sedleian chair. During his career, he wrote several books and articles on medicine and his work on the anatomy of the brain and nervous system, based on his own dissections, remains very celebrated. Willis provided the description of the autonomic nervous system, the spinal cord, the vasculature at the base of the brain (circle of Willis) and the cranial nerves, including the accessory nerve (Willis' nerve)[9].

Willis, as physician, belonged to the Iatrochemical School of medicine which believed that chemistry was the basis of human function. Concerning diabetes, in his Pharmaceutice rationalis, Willis devoted a chapter to the "pissing evil". He commented on the sweetness of the urine in diabetic patients, coining also the term mellitus[10]. It was actually a rediscovery, as in the 7th century BC the Indian physician Sushruta mentioned the sweet urine of the disease but this work apparently was unknown to Willis. So, he was the first European medical writer who mentioned the sweet taste of the urine in diabetes mellitus. It seems that he saw several cases of diabetes mellitus and he believed that it was due to an affection of the blood rather of the kidneys. He attributed it to the eating habits and psychological status "an ill manner of living and chiefly an assiduous and immoderate drinking of cider, beer and sharp wines; sometimes sadness, long grief". He recognized also diabetic neuropathy in the sufferers describing it as "stinging and other…frequent contractions or convulsion, twinging of the tendons and muscles and other disturbances"[9-11].

Concerning the sweet taste of the urine, he reported a case of "a certain noble earl" who suddenly "became much inclined to excessive pissing… in the space of twenty-four hours, he voided almost a gallon and a half of limpid, clear, and wonderful sweet water, that tasted as if it has been mixed with honey". Therapeutically he considered beneficial for the disease a "thickening and moderately cooling diet and cordials" and he mentioned that slimy vegetables, rice, white starch may improve patient's status. He also suggested a milk drink which was distilled with cypress tops and egg whites, two

**Figure 2 Portrait of the French physiologist Claude Bernard.** (Source: Wellcome Library, London).

powders (a mixture of gum arabic and gum dragant), rhubarb and cinnamon. Following Willis' therapeutic advices, patient's condition improved in a month but immediately after his recovery, he returned to his past dietary habits[9].

However Willis could not explain "why the urine is wonderfully sweet like sugar or honey". The explanation was given 100 years later, by another English physician, Matthew Dobson (1732-1784) of Liverpool, who experimentally demonstrated the presence of sugar in urine. He actually boiled urine to dryness and noticed that the residue, a crystalline material, had the taste of brown sugar[11].

## CLAUDE BERNARD'S (1813-1878) BRILLIANT DISCOVERY ON THE GLYCOGENIC ACTION OF THE LIVER

Born to a poor family in Beaujolais region, south of France, Claude Bernard at the age of 19 was apprenticed to an apothecary. His passion for the theatre led him to write two plays La Rose du Rhône and Arthur de Bretagne but soon after arriving to Paris, he was discouraged by the literary critic and politician Saint-Marc Girardin (1801-1873) who counseled him to enroll in medicine. In Medical School of Paris, Bernard was not considered a brilliant student and unwilling to practice medicine, he was appointed assistant to the Professor of Physiology and pioneer of experimental physiology François Magendie (1783-1855). However, Bernard's research career was very successful. In 1854, he became member of the Academy of Sciences and later on he succeeded Magendie to the chair of experimental physiology at the College de France. The Emperor Napoleon Ⅲ admired him so much that created two laboratories for him and made him a Senator. Among Bernard's several discoveries we may cite: the vasomotor innervation, the principle of physiological determinism, the concept of internal secretion, the concept of milieu intérieur or internal environment (meaning the interstitial fluid, and its physiological capacity to ensure protective stability for the tissues and organs), the nature and function of curare, carbon monoxide and other poisons (Figure 2). Unfortunately, the only way to understand and discover all these phenomena, promoting our knowledge to physiology, was through animals' vivisections. This was the reason for his wife to divorce him and join with his children the antivivisection movement, campaigning actively on the issue[12].

Bernard's contribution in the study of metabolism and diabetes remains leading. In 19$^{th}$ century, scientists hypothesized on the role of pancreas in the physio-pathology of diabetes as they found in the post-mortem examination of the diseased, atrophic or stone filled pancreases. However, as they believed that pancreas was an exocrine organ, they interpreted these post-mortem findings as a chance phenomenon. During that period the French experimental physiologist, Claude Bernard decided to test this hypothesis[1,12].

At the beginning, he falsely believed that "diabetes was a nervous affection of the lungs". However, during an experiment, he injected grape sugar into the jugular vein of a dog, extracting at the same time blood from the carotid artery. This blood contained a large amount of sugar and he realized that glucose was not destroyed in the lungs, because blood must pass by these organs in order to move from the jugular vein to the carotid artery. He was then fed dogs on a carbohydrate-rich diet, the blood from the hepatic veins and vena cava contained sugar which was not destroyed in the liver and was also present in heart ventricles, so the theory of lungs' role in diabetes was rejected. In further experiments, Bernard proved that animal blood contains sugar even if it is not supplied by food. Testing the theory that sugar absorbed from food was destroyed when it was passing through tissues, Bernard put dogs in carbohydrate diet and killed them immediately after feeding. To his surprise he observed large amounts of sugar in hepatic veins. The same observation was done in the control group, animals that were fed only by meat. He then moved to the analysis of liver tissue samples and in every liver he examined he found large quantities of glucose which was missing from other organs. He concluded that liver was storing a water insoluble starchy substance that he named glycogen which was converted into sugar or glucose and secreted into the blood. He assumed that it was an excess of this secretion that caused diabetes[13,14].

Moving toward, Bernard demonstrated the connection between the central nervous system and diabetes. Using a needle, he stimulated the floor of the fourth brain ventricle and produced temporary "artificial diabetes" which lasted less than one day. He named this procedure piqûre diabétique and linked for the first time glucose homeostasis and the brain to the pathogenesis

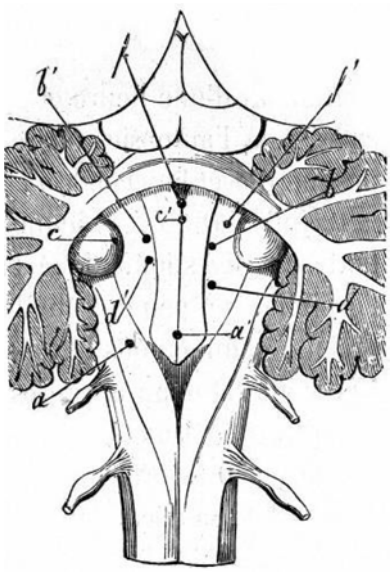

**Figure 3 Sites of punctures of 4th ventricle from Bernard's book «Leçons sur la Physiologie et la Pathologie du Système Nerveux», 1858.** (Source: Wellcome Library, London).

**Figure 4 The Nobel laureate Frederick Banting in his laboratory with a dog.** (Source: Wellcome Library, London).

of diabetes[15] (Figure 3).

The work of Claude Bernard on glycogenic action of the liver illuminated the pathway of gluconeogenesis and promoted the study of diabetes.

## OSKAR MINKOWSKI (1858-1931) AND JOSEPH VON MERING (1849-1908): THE DISCOVERY OF "PANCREATIC DIABETES"

A turning point in the history of diabetes mellitus took place in 1889 after the experiments of Minkowski and von Mering.

In 1886, three years before their first meeting, von Mering discovered that phlorizin, a glucoside, could cause transient glucuresis. In 1889, while von Mering was working in Hoppe Seyler's Institute at the University of Strasbourg, Minkowski, assistant at that time to the German leading authority on diabetes Professor Bernard Naunyn (1839-1925), he visited the Institute to look at some chemical books of the library. They met accidentally and talked about Lipanin, an oil containing free fatty acids and von Mering used to administrate to patients suffering from digestive disturbances. Minkowski was not in favor of Lipanin intake and then their conversation turned on whether the pancreas had a role in digestion and absorption of fats. As a result of the discussion, the two men decided the same evening to perform a pancreatectomy in a dog in Naunyn's laboratory. The animal remained alive and was closely observed by Minkowski, as von Mering left urgently to Colmar because of a family issue. Soon after the operation, the dog developed polyuria. Minkowski examined the urine and found that it contained 12% sugar. Initially Minkowski believed that the dog developed diabetes due to the fact that von Mering had treated it for a long time with phlorizin. So he repeated the pancreatectomy in three more dogs which had no sugar in their urine previous to operation and all of them developed glycosuria[13,16].

Furthermore Minkowski implanted a small portion of pancreas subcutaneously, in depancreatized dogs, and observed that hyperglycemia was prevented until the implant was removed or had spontaneously degenerated[13].

Minkowski and von Mering experiment demonstrated that pancreas was a gland of internal secretion important for the maintenance of glucose homeostasis. They also paved the way for Banting and Best to conduct their experiments and to meet with success.

## FREDERICK BANTING (1891-1941), CHARLES BEST (1899-1978), JAMES BERTRAM COLLIP (1892-1965) AND JOHN MACLEOD (1876-1935): THE DISCOVERY OF INSULIN

In 1923 the Nobel Prize in Medicine was awarded to Frederick Banting and John MacLeod for the discovery of insulin. It was actually a story of success that provoked a great scientific conflict.

Frederick Banting was a young Canadian surgeon, who was admitted into the laboratory of the eminent biochemist, interested in diabetes, Professor John Macleod, at the University of Toronto[13]. In 1920, Moses Barron, physician in Minnesota, published an article on "The relation of the islets of Langerhans to diabetes, with special reference to cases of pancreatic lithiasis[17] which was mentioning that the continuation of experiments of Minkowski and von Mering could lead to

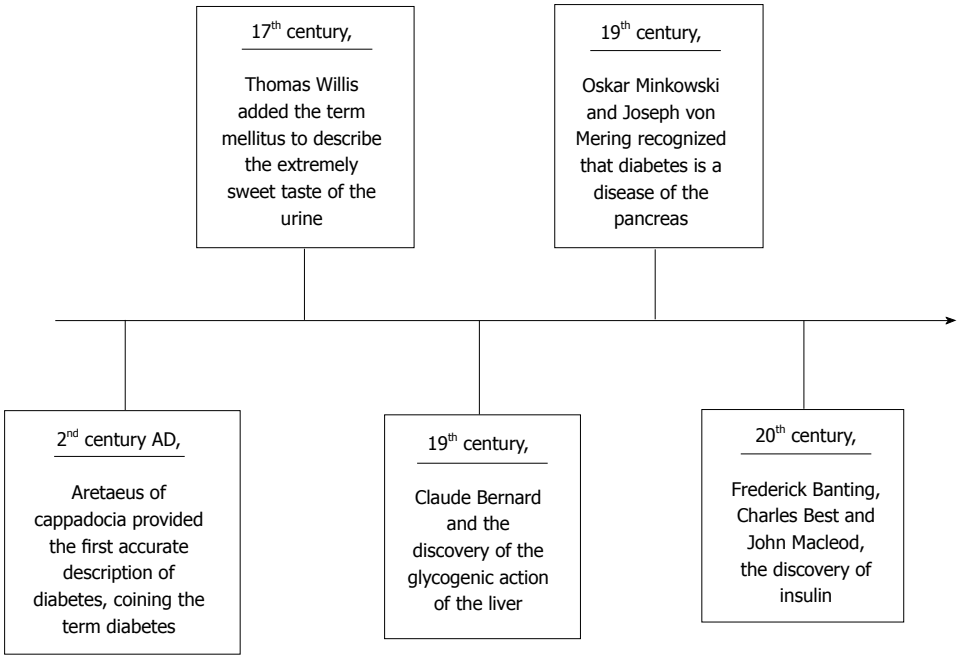


**Figure 5 Timeline table presenting the main contributors in the history of diabetes mellitus.**

the discovery of a substance capable to control diabetes. Influenced by this article, Banting focused on the study of diabetes[13]. During that period the distinguished English physiologist Ernest Starling (1886-1927) was mentioning: "We don't know yet how the pancreas affects sugar production or utilization in the same animal. It is generally assumed that it secretes into the bloodstream a hormone which may pass to the tissues and enable them to utilize sugar or pass to the liver and inhibit the sugar production of this organ… but we have been unable to imitate the action of the pancreas still in vascular connection with the body, by injection or administration of the extracts of this organ"[18].

On 16 May 1921, Banting started to collaborate with Charles Best, a young medical student. Experimenting in dogs they initially ligate the pancreatic ducts, achieving atrophy of the exocrine region and almost ten weeks later they removed dog's degenerated pancreas. They crushed the atrophied pancreatic glands in a cool mortar and froze it in salt water. Then the mass was ground down and added to 100 mL of physiological salt. Afterwards, they administrated 5 mL of this extract intravenously to a depangreatized dog. Within 2 h its blood sugar had considerably dropped. They repeated several times the experiment with other diabetic dogs, gaining similar results and they experimented also with fetal calf pancreas using different ways of administration such as subcutaneous and rectal[19,20] (Figure 4).

At the end of 1921 the skilled chemist James Collip joined the team and developed a better extraction and purification technique. Obtained substance was initially named by the team insletin and later on by MacLeod insulin[13].

The next step was to test insulin in humans. So on 11 January 1922, insulin was administrated to Leonard Thompson a 14-year-old boy treated for diabetes in Toronto Hospital[13]. It's worth mentioning that after the introduction of Apollinaire Bouchardat's (1806-1886) pioneering dietary treatment for diabetes, physicians repeated in several generations of diabetics his motto: "mangez le moins possible" (eat as little as possible)[21,22]. Thomson was also following a strict fasting diet proposed by Frederick Madison Allen (1879-1964) and he was in critical state. He received 15 mL of insulin, injected in his buttock but he developed abscesses at the injection site and became even sicker. Collip further improved the quality of insulin and on January 23, Thompson received a second injection. The results were excellent. His blood glucose from 520 mg/dL fell to 120 mg/dL in 24 h and urinary ketones disappeared. Thompson continued the treatment with insulin and lived another 13 years. He died of pneumonia at 27 years old[13]. Similar is the story of Elizabeth Hughes Gossett (1907-1981). Daughter of the United States politician Charles Evans Hughes, Elisabeth was diagnosed with diabetes at age 11. Initially she was also treated by Allen and in August 1922 began the use of insulin. She survived, graduated from College, got married, had three children and died suddenly of a heart attack at 74 years old[23].

The pioneering work of Banting and Best saved millions of lives and diabetics started to live a normal life. Lilly Pharmaceutical Company collaborated with the two scientists and in 1923 introduced Iletin, the world's first commercially available insulin product[13].

However in 1923 the Nobel Committee decided to award Banting and MacLeod for insulin's discovery. Banting became furious as he believed that he should share the prize with Best instead of MacLeod and he decided to share with Best his cash award. In his turn,

MacLeod shared also his award with Collip[13].

Another black spot in the history of insulin discovery was also the discovery of pancreatin, an extract of bovine pancreas discovered by the Romanian Professor of Physiology Nicolae Constantin Paulescu (1869-1931) in 1916, published a few years later because of the war in 1921 and patented in April 1922. Even if Paulescu was the first to provide a detailed demonstration of the antidiabetic and antiketogenic effect of a pancreatic extract, pancreatine was not used in humans and passed over silently[24].

A crucial step in the history of diabetes has been completed. Over the next years insulin purification methods improved and new insulin formulations were developed such as Protamine–zinc insulin, a long-acting insulin in 1930s, neutral protamine Hagedorn in 1940s and Lente series in 1950s[13].

## CONCLUSION

For more than 3000 years physicians quested the causes and treatment of diabetes mellitus (Figure 5). However, an important progress has been made over the last two centuries thanks to the development of chemistry, physics and pharmacology. Over the next years scientists continued to make significant discoveries: The structure of insulin was delineated in 1955 by the Nobel laureate Fred Sanger (1918-2013); in 1967 proinsulin was discovered by Donald Steiner (1930-2014) and with his colleagues he produced the radioimmunoassay for C-peptide which is used today to measure endogenous insulin production; in the same year, the first pancreas transplant in a human was performed by William Kelly, Richard Lillehei (1927-1981) and colleagues at the University of Minnesota; in 1972 the U100 insulin was introduced to promote better accuracy in administration; ten years later, in 1982, recombinant human insulin became available and in early 1990's insulin pen delivery devices become popular following by the discoveries of short (1996) and long (2001) acting insulin analogues[1].

Since biotechnology helps medicine to progress, nobody knows what the future will bring. We are sure of just one thing: History of diabetes is being still written.

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SYSTEMATIC REVIEWS

# Tipping the balance: Haemoglobinopathies and the risk of diabetes

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## Abstract

**AIM:** To establish a link between the risk of diabetes with haemoglobinopathies by examining available evidence of the effects of iron and blood glucose homeostasis from molecular to epidemiological perspectives.

**METHODS:** A systematic literature search was performed using electronic literature databases using various search terms. The International Diabetes Federation World Atlas was used to generate a list of populations with high rates of diabetes. PubMed, Scopus and Google Scholar were used to identify which of these populations also had a reported prevalence of haemoglobin abnormalities.

**RESULTS:** Abnormalities in iron homeostasis leads to increases in reactive oxygen species in the blood. This promotes oxidative stress which contributes to peripheral resistance to insulin in two ways: (1) reduced insulin/insulin receptor interaction; and (2) β-cell dysfunction. Hepcidin is crucial in terms of maintaining appropriate amounts of iron in the body and is in turn affected by haemoglobinopathies. Hepcidin also has other metabolic effects in places such as the liver but so far the extent of these is not well understood. It does however directly control the levels of serum ferritin. High serum ferritin is found in obese patients and those with diabetes and a meta-analysis of the various studies shows that high serum ferritin does indeed increase diabetes risk.

**CONCLUSION:** From an epidemiological standpoint, it is plausible that the well-documented protective

effects of haemoglobinopathies with regard to malaria may have also offered other evolutionary advantages. By contributing to peripheral insulin resistance, haemoglobinopathies may have helped to sculpt the so-called "thrifty genotype", which hypothetically is advantageous in times of famine. The prevalence data however is not extensive enough to provide concrete associations between diabetes and haemoglobinopathies - more precise studies are required.

**Key words:** Diabetes; Ferritin; Haemoglobinopathy; Iron metabolism; Malaria



**Core tip:** Are diabetes and haemoglobinopathies linked? There is strong evidence to suggest that the processes involved in both iron and blood glucose homeostasis interact with one another. Metabolic disorders involving iron appear to contribute to the pathological process of diabetes at least on a cellular level. This article also examines prevalence data of diabetes and various haemoglobinopathies in certain populations to establish whether there is an association from an epidemiological perspective.

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## INTRODUCTION

There are a number of postulated theories that suggest that there were once evolutionary benefits of certain gene variants that are known to cause disease in modern populations. One such association is demonstrated by the protective nature of Sickle-cell trait in terms of the interruption of the life cycle of *Plasmodia*, which lessens the impact of malaria infection on an individual with such a phenotype[1]. It does not seem unreasonable to suggest that there may be other associations that are yet to be discovered. The evolutionary advantages of having higher blood glucose concentrations have been suggested by the "thrifty genotype" hypothesis, *i.e.*, peripheral insulin resistance acting to ration energy in times of famine[2]. This article focuses on the associations between iron metabolism and type 2 diabetes mellitus by examining the available evidence. The pathological link between haemoglobin abnormalities and diabetes is investigated in addition to the molecular mechanisms that may be involved. The prevalence of type 2 diabetes has risen in populations who live in regions with antecedentally high rates of malaria infection and in ethnic groups who have emigrated from these areas[3,4]. Prevalence data of haemoglobinopathies, iron transport abnormalities and diabetes are examined in order to establish whether populations with high rates of diabetes are more likely to have haemoglobin abnormalities.

## MATERIALS AND METHODS

A systematic literature search was performed using electronic literature databases, PubMed, Web of Knowledge and Cochrane Library. The search terms used included: "diabetes", "diabetes mellitus", "diabetes mellitus type 2", "iron", "free radicals", "glucose tolerance", "insulin resistance", "insulin", "resistance", "sensitivity", "hepcidin", "ferritin". Relevant references from selected articles were also reviewed. The International Diabetes Federation World Atlas was used to generate a list of populations with high rates of diabetes. PubMed, Scopus and Google Scholar were used to identify which of these populations also had a reported prevalence of haemoglobin abnormalities.

## RESULTS

### *Putative link between haemoglobin metabolism and diabetes*

**Oxidative stress, iron and diabetes:** The production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) due to iron overload in humans has been attributed to the Fenton Reaction. This occurs due to the ability of iron to convert between its two oxidative states, $Fe^{2+}$ and $Fe^{3+}$[5]. Alternative proposed mechanisms include the Haber-Weiss reaction, with haem iron acting as a catalyst and $Fe^{2+}$ as a reactant[6]. Antioxidants and detoxifying enzymes are required to maintain careful control of ROS and RNS production. Iron overload can tilt this balance, leading to oxidative stress[6]. Oxidants have in turn been shown to cause the release of catalytic iron resulting in the formation of yet more ROS and RNS forming a vicious cycle[7]. Oxidative stress is one mechanism speculated to be linked to insulin resistance and abnormal glucose tolerance, as a novel explanation of the link between diabetes and iron overload.

Pancreatic β-cells in fact show particular sensitivity to oxidative stress due to their low expression of antioxidants such as catalase and SOD2[8]. The resulting β-cell dysfunction as a consequence of this stress causes decreased expression of transcription factors required for cell maintenance and insulin production[8]. Further research has demonstrated that circulating insulin is also directly affected by ROS, affecting the ability of insulin to bind to the insulin receptor[9]. The combination of these factors consequently leads to hyperglycaemia and ultimately, the development of diabetes.

Homeostatic mechanisms for preventing damage from iron overload include both the regulation of cytosolic iron by binding to iron regulatory proteins (IRP) and production of the peptide hormone Hepcidin[8].

**Table 1 Comparison of studies examining Hepcidin, Prohepcidin and Serum Ferritin concentrations in individuals with type II diabetes**

| Ref. | No. of patients with type II diabetes | No. of total participants | Hepcidin concentration | Prohepcidin concentration | Serum Ferritin concentration |
|---|---|---|---|---|---|
| Aso *et al*[16], 2010 | 104 | 169 | - | Significantly lower than control | Significantly higher than control |
| Jiang *et al*[24], 2011 | 34 | 64 | Significantly higher than control | - | Significantly higher than control |
| Guo *et al*[25], 2013 | 555 | 1259 | No significant difference from control | - | Significantly higher than control |
| Sam *et al*[26], 2013 | 33 | 66 | Significantly lower hepcidin than control | - | Not significantly higher than control |

Binding of IRP results in a decrease in iron uptake into the body and an increase in the translation of ferritin, a molecule that sequesters iron within cells[8]. High serum ferritin levels are associated with obesity, metabolic syndrome and cardiovascular risk and more recent studies have demonstrated it to be directly associated with diabetes[10-12]. Care must be taken however in attributing causality to this relationship. Diabetes is known to be a chronic inflammatory state, and this finding may simply be explained by the fact that ferritin is an acute phase reactant and therefore simply produced as a result of inflammation[13].

Hepcidin has been shown to inhibit cellular iron efflux by binding to ferroportin, an important iron exporter, causing the internalisation and degradation of iron[14,15]. Subsequently, hepcidin decreases intestinal iron absorption and prevents the release of iron from macrophages[16]. The hepcidin-ferroportin axis is essential to maintaining iron homeostasis, however is still not completely understood[17]. Hepcidin is modulated by its inversely proportional relationship to both serum and tissue iron, with iron concentrations being inversely proportional to hepcidin concentration. This balance is essential to maintain iron as demonstrated clinically in patients with hereditary hemochromatosis who have low hepcidin levels and hence have toxic accumulation of iron[18].

The synthesis of hepcidin is mainly within hepatocytes, but has also been noted in pancreatic β cells and the adipose tissue of obese patients[19,20]. This may suggest that pancreatic β cells also have a role in iron metabolism in addition to the regulation of glucose and insulin[19]. Whilst several studies have investigated levels of circulating hepcidin or prohepcidin (a precursor of hepcidin) in patients with diabetes (Table 1), there is currently no consensus or large scale-studies available, and data relating to the role of hepcidin in this context is limited. Cell culture studies have revealed that glucose induces secretion of hepcidin in INS-1E cultures (a pancreatic β cell model) yet has no effect on HepG2 cell cultures (a hepatocyte model)[21]. In contrast, insulin up-regulates hepcidin secretion in HepG2 cell cultures. There was no data found for the effect of insulin on hepcidin secretion by pancreatic β cells[22]. A single murine study looked at hepcidin activity during starvation. It proposed that the increased hepcidin secretion seen in such states has a role in preserving tissue iron and supporting gluconeogenesis in the liver[23]. As gluconeogenesis is abnormally induced in obese individuals and those with diabetes, a link between diabetes and hepcidin is possible[23]. Whilst it seems likely that hepcidin has a role in the glucose-insulin axis, no firm conclusions are possible with the data currently available. Further exploration of the role of hepcidin could explain whether an elevated serum ferritin is the likely cause or effect of the chronic inflammation seen in diabetes.

The link between abnormal iron metabolism and diabetes is established in those with Sickle-cell disease and haemochromatosis[27,28]. However, the effect of iron intake on the risk of healthy individuals developing diabetes and its subsequent clinical progression is much less clear.

Haemochromatosis is known to result from the dysregulation of the body's finely balanced iron metabolism[29]. The resulting free iron is known to be toxic when present in sufficiently high concentrations although the exact mechanisms behind its role in both health and disease are still not fully understood. The ubiquitous nature of iron *in vivo*, from oxygen transport and energy metabolism to DNA synthesis, explains the systemic and wide ranging tissue types affected by this disease. Traditional explanations of the resulting diabetes have cited iron as a purely diabetogenic influence[30]. However, a recent paper by Abbas *et al*[31] challenges the traditional thinking regarding the role that increased iron deposition plays in haemochromatosis. Indeed, iron overload in hereditary haemochromatosis was found to exhibit both pro-diabetic influences, mediated *via* beta-cell toxicity as well as an anti-diabetic effect caused predominately by weight loss[31].

Research targeted at a link between abnormal iron metabolism and diabetes in those who are otherwise healthy has repeatedly produced conflicting results. Jiang *et al*[32] conducted a prospective study that followed up a cohort of initially healthy males for 12 years. Total haem and/non-haem iron intake was compared between those who developed diabetes in this time period, and those who remained healthy. Only haem iron was positively associated with diabetes although other lifestyle factors could not be excluded as contributors[33]. This result has been backed up by similar research, including data from the Nurses' Health

Study Ⅱ and other large cohort studies[34,35].

In contrast, an African study demonstrated that there was no link between serum ferritin and diabetes prognosis in those with patients without additional health complications[36]. However, with a small sample size ($n$ = 60), and the fact that these were not newly diagnosed diabetics this conclusion must also be treated with caution. A study in India concluded there was no link between raised serum ferritin and the risk of developing diabetes. However, it did not look at any other indices of iron status, which would have allowed comparison with the current literature[37].

Orban *et al*[33] recently attempted to make sense of these conflicting results with a meta-analysis of studies of indices of iron status in those without haemochromatosis or thalassemia[32]. It concluded that a significant link between a raised ferritin level and an increased risk of diabetes does indeed exist. Other indices such as transferrin saturation and soluble transferrin receptor number were also implicated but a methodology which failed to address the confounding effect of inflammation and a low statistical power means these conclusions must be met with caution[32].

It has been highlighted that these results indicate the very immediate need for further, high quality research regarding the effect of iron intake on the progression of diabetes in those without abnormal iron metabolism[38]. For example, looking at the effect of iron supplementation on diabetes progression in newly diagnosed patients. To date only the risk of developing the disease has been looked at in detail epidemiologically. Additionally, the mechanistic studies are generally in their infancy, *i.e.*, are only based on animal models at this stage. This area of research would need to be advanced to human based studies to yield more significant data.

### *Epidemiology of Fe transport/haemoglobin abnormalities and association with diabetes in populations*

The worldwide distribution of the common haemoglobinopathies coincides with that of malaria, and indeed confers resistance from its more severe expressions[1,39]. Inherited haemoglobin disorders (Sickle-cell disorders and thalassaemias) were originally characteristic of the tropics and subtropics but are now common worldwide due to migration[40]. However, the main regions with the highest rates of Sickle-cell disease are sub-Saharan Africa, the Mediterranean[41], the Middle East[42,43] and the Indian subcontinent. Additionally, the Sickle-cell gene variants are extremely common in some of the Caribbean Islands and in North America[44].

The prevalence of diabetes in sub-Saharan Africa is reported as being between 1% (rural Uganda) and 12% (Nairobi)[45]. A paediatric study of 860 individuals in Western Kenya reported 38.5% were heterozygous and 9.5% homozygous for α-thalassaemia. Sickle-cell trait was present in 17.2% and Sickle-cell disease in 1.8%[46]. This demonstrates a relatively high prevalence of both diabetes and haemoglobinopathies, calling for the need for further investigation to directly compare diabetes and haemoglobinopathies in each of these populations. Prevalence of diabetes in India is 9.1%, with the cumulative gene frequency of haemo globinopathies being 4.2%, with large variation between different ethnic groups[47]. Again, direct study of both conditions in these individual ethnic groups is needed in order to draw more meaningful comparison. Turkey is of particular interest as the prevalence of diabetes is 14.8%, but Sickle-cell disease is only found in 0.3%, which suggests much less of a correlation than that seen in India and Africa. However, in some areas of Turkey, (*i.e.*, Çukurova) the prevalence of carriers of HbAS is as high as 44%[48,49]. A similar affect has been reported in Madang in Papa New Guinea, where 97% of the population tested were either heterozygous or homozygous for α-thalassaemia[50]. The overall prevalence of diabetes in Papa New Guinea is 5.2%[51], however it would be interesting to examine the populations of Madang and Çukurova for diabetes prevalence specifically due to the extremely high rates of α-thalassaemia and HbAS. The United States provides interesting data. The overall prevalence of diabetes is 9.2%, with 13.2% of African Americans affected[52]. The highest rates of diabetes in the United States are actually amongst American Indians and Alaskan natives (15.9%)[52], where the prevalence of Sickle-cell disease is 36.2/100000 live births, making these ethnic groups the third most affected by Sickle-cell disease behind African Americans (289/100000) and Hispanics (89.1/100000)[53,54]. Hb-E occurs widely throughout the eastern half of the Indian subcontinent, Bangladesh, Myanmar, and East and Southeast Asia. Most notably in the Northern parts of Thailand and Cambodia, where the region is referred to as the "Hb-E Triangle" where up to 70% are carriers. The prevalence of diabetes in these areas is 8.5% (Thailand)[55] and 2.6% (Cambodia)[56].

Although, on the whole, it is difficult to determine any firm correlations using the above sources, the existing data certainly summons enough intrigue to warrant further investigation.

## DISCUSSION

Examining the epidemiological evidence for an association between diabetes and the various haemoglobinopathies is not straightforward. The main issue is the complex interplay of various environmental and biological factors that all contribute to the development of diabetes, making a clear association between certain factors difficult to prove. There is clear evidence on a molecular level of an interaction between glucose homeostasis and haem abnormalities, however the epidemiological perspective remains unclear due to a lack of specific studies in this area. Focussed diabetes prevalence data from the groups with extremely high carrier rates of the various haemoglobinopathies would be extremely beneficial, as a link between the molecular

evidence and the epidemiological picture could be demonstrated. Other issues include the large number of individuals with diabetes who are undiagnosed. Improvements in screening and healthcare education programs seem to be the answer here, although these are not without their own problems. The Center for Disease Control and Prevention estimates this figure to be 8.1 million people (27.8% of those with diabetes) in the United States[53], making true prevalence data difficult to obtain. It remains plausible however that in the face of various selective pressures there was once an evolutionary advantage in having a higher blood glucose level. This could help to explain why there are a number of ethnic groups who are at greater risk of developing diabetes than others. It is also possible that these genetic predispositions to higher blood glucose levels developed in tandem with the haem abnormalities that are known to be protective against malaria. However with a lack of studies directly examining the two conditions, a concrete association is difficult to prove.

## COMMENTS

### Background

A putative pathophysiological mechanism exists between diabetes and blood born disorders. These processes involve both iron and blood glucose metabolism and there is a high potential for the two to interact with one another.

### Research frontiers

Metabolic disorders involving iron contribute to diabetes on a cellular level. Evidence at a clinical or population level is less clear and is reviewed here.

### Innovations and breakthroughs

The evidence reviewed here provides a putative link between diabetes and haemoglobinopathies which carries clinical ramifications (with respect to risk) for populations that have an antecedental risk of blood born disorders. The role of iron metabolism and its impact on diabetogenic risk is also considered here.

### Peer-review

This article is based on a literature search, focusing on correlations between iron metabolism and type 2 diabetes, and on epidemiological data in search for a possible link between diabetes and haemoglobinopathies. It is a potentially useful paper for discussion of an important subject that could be of use to the clinicians and researchers in the field as an overview, where many studies are compared with their strong and weak points, and suggestions are given.

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