



## Review paper

# Diabetes – the history of research and treatment

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### ABSTRACT

**Introduction:** The history of diabetes is a fascinating journey – from the times before the current era to the modern day. This history is rich in a lot of discoveries, advancements in science and technology, renowned scientists, doctors and their achievements as well as challenges.

**Aim:** To present the history of research on diabetes and its treatment.

**Material and methods:** A review of literature concerning the history of research on diabetes and methods of its treatment.

**Results and discussion:** First descriptions of diabetes, today a well-known disease, date back to ancient Egypt; its mysteries were discovered by Hippocrates, Aretaeus of Cappadocia and an Arabic doctor Avicenna. The term ‘diabetes mellitus’ was first used in 1797 and the greatest breakthrough in research on diabetes took place in 1922, when insulin was discovered. This revolutionised the treatment, yet led to the development of a number of chronic vascular complications.

**Conclusions:** At present, diabetes – as a non-communicable disease – is perceived by the World Health Organisation as an epidemics, and only getting to know its history can mean having complete knowledge about the disease.

## 1. INTRODUCTION

Since its origin the world has been pestered by a number of diseases. A long time ago these were acute infectious diseases, such as plague, cholera, smallpox, which left death in their wake. However, already since the ancient times, there was a disease known as ‘diabetes’ from the Greek ‘siphon’ which denoted ‘the flow of water through the organism’ of the patient. This disease also unavoidably led to death.<sup>1</sup> In line with changes in lifestyle, especially dietary habits, we have witnessed a rapid increase in the incidence of obesity in developing societies and in the progression of metabolic disorders related to obesity.<sup>2</sup> Currently, these are not infectious but civilizational diseases that lead to disabilities and death, and diabetes has assumed a form of epidemics.<sup>3</sup>

## 2. AIM

To present the history of research on diabetes and its treatment.

## 3. MATERIAL AND METHODS

A review of publications from around the world, including European and Polish ones, has been conducted with focus on history of research on diabetes and methods of its treatment.

## 4. RESULTS AND DISCUSSION

### 4.1. From diagnosis to detection of insulin

Diabetes has been known for thousands of years. First reports concerning its symptoms come from ancient Egypt, from 3500 BCE. The disease was initially diagnosed as a urinary system condition, due to polyuria, which was its main symptom presentation. The first clinical overview can be read in the Ebers Papyrus from 1530 BCE, which was found in 1867 in an Egyptian tomb. Another similar description on papyrus was found in Dayr al-Barsha in 1899. There was also located a skeleton of a man who lived in 2055–1650 BCE and it was suspected he died of diabetes. Charaka, a doctor who lived in India between 800 BCE and 200 BCE, described the urine of diabetic patients as ‘attracting ants and flies’ and differentiated between diabetes in obese older people and slim younger people who died soon after the diagnosis. In Greece, Hippocrates described a disease which consumed the organism and demonstrated itself in an increased frequency of urination. However, for the history of diabetes research it is Aretaeus of Cappadocia who can be seen as the main figure. He was a doctor of Greek origin who worked in Rome and who was first to use the word ‘diabetes’ from the Greek ‘siphon,’ which denoted ‘the flow of water through the organism’ of the patient. He is the author of the first full description of symptoms of diabetes as a chronic

disease which caused ‘loss of body weight and body members together with urine’ in people who had unquenchable thirst, dry lips, dry body and lived short. In another part of the Arabic world, Avicenna described such symptoms found in diabetic patients as: increased appetite, mental exacerbation, impotence and diabetic gangrene.<sup>2</sup> The term ‘diabetes mellitus’ (DM) was first used in 1797 by John Rollo.<sup>4</sup> In turn, in 1841 Karl Trommer invented a method known as the quantitative and qualitative assay of glucose.<sup>5</sup> In 1889 Minkowski and von Mering, having performed pancreatectomy in dogs, noticed glucosuria, which confirmed that there was a correlation between diabetes and Langerhans islands.<sup>6</sup> This experiment was described by Paul Langerhans in 1869.<sup>7</sup> Insulin was discovered as late as in 1922 by Banting, Macleod, Best and Collip, who received the Nobel Prize in physiology for their discovery.<sup>8</sup> Many years later, in 1951, Frederic Sanger was awarded the Nobel Prize for discovering the chemical pattern of an insulin molecule.<sup>9</sup>

### 4.2. From human insulin to modern insulin analogues and anti-hyperglycaemic medicines

Frederick Grant Banting of the University of Toronto and a medical student Charles Herbert Best successfully injected insulin for the first time on January 23, 1922. It was Leonard Thompson, a 14-year old DM type 1 (T1DM) patient, who had the life-saving medicine administered. The patient received 5 mL, then 10 mL after 24 h, which led to a decrease in glycaemia from 520 mg/dL to 120 mg/dL.<sup>10</sup>

The history of diabetology in Poland had its beginning only two years after the first successful administration of insulin, in 1924. In September 1923 in Warsaw the National Institute of Hygiene (NIH) was established on the initiative of Ludwik Rajchman, who later founded UNICEF. Thanks to the work of Kazimierz Funk, production of insulin started in January 1924, reaching 315 650 units by the end of the year. Poland thus joined the group of European countries, such as Denmark, United Kingdom, Spain and the Netherlands, which went on to produce the hormone.<sup>8</sup> Funk was also the author of first scientific publications in Poland on the effect of insulin on phosphates metabolism. He left Warsaw in 1927 because of the unstable political situation in Poland, and Tomasz Spasowicz took over from him as a person in charge of Polish insulin production. The mass production commenced in 1929, and thanks to new laboratory equipment the quantity and quality considerably increased. This was confirmed in the first academic publication devoted to Polish insulin, whose author, Józef Grott, reports that insulin produced in the NIH was of similar quality as foreign preparations.<sup>11</sup> In 1938 in the NIH Spasowicz started the production of protamine zinc insulin, which continued throughout the Second World War<sup>12</sup>.

In the 1960, lente preparations were made mixing insulin and an acetate buffer with additional zinc. In the subsequent years, thanks to the technology of *Bacterium coli* and then yeast DNA recombination, human insulins were produced. Mastering Roentgen crystallography led to research on analogues of insulin. The first analogue which soon entered clini-

cal applications was insulin lispro, then insulin aspart, and then insulin glulisine.<sup>13–15</sup> The next important step in diabetes treatment was introducing long-acting almost ‘peakless’ analogues, such as insulin detemir and insulin glargine.<sup>16,17</sup> A breakthrough consisted in introducing a new generation basal insulin degludec, with a very long acting time, which exceeds 42 h. In a number of studies assessing clinical pharmacology it was shown that this insulin is characterised by a flat and stable pharmacokinetic and pharmacodynamic profile at steady-state in diabetic patients. The first patent was issued in Europe in 2013, in Poland it appeared at the end of 2015. The most recent preparation available in Poland since the beginning of 2017 is insulin glargine in a concentration three times higher than the traditional long-acting analogue, which ensures stable release of particles from the precipitate.<sup>18–20</sup>

The 20th century was also an era of development in anti-hyperglycemic medicines. Derivatives of sulfonylurea, derivatives of biguanides and  $\alpha$ -glucosidase inhibitors were discovered, respectively in the 1940s, 1950s and 1980<sup>21</sup>. In the 1960s it was found that insulin secretion in response to oral glucose supply is much stronger than when given intravenously – it is an incretin effect. Under the influence of orally administered glucose, glucagon-like peptide-1 (GLP-1) is secreted by the cells of the intestinal mucosa.<sup>22</sup> This hormone increases the secretion of insulin by the pancreas. GLP-1 is rapidly inactivated by the enzyme dipeptidyl peptidase 4 (DPP-4).<sup>23</sup> Already in the 1880s, Nauck and his colleagues showed that the incretin effect works less effectively in patients with T2DM<sup>24</sup>. The above pathomechanisms prompted researchers to look for methods for the practical application of incretin pathway mediators and the 21st century saw implementation of medicines like: GLP-1 receptor agonists and DPP-4 inhibitors<sup>25</sup>.

Phlorizin discovered in 1835, was the first historical inhibitor of sodium glucose co-transporters (SGLT), but it had many side effects<sup>26</sup>. Other new orally administered anti-hyperglycaemic medicines – synthetic SGLT-2 inhibitors have a high selectivity and causes only glucosuria.<sup>25</sup>

### 4.3. Challenges of contemporary diabetology

Before insulin was discovered, diabetic patients had been treated almost only with dietary measures and died very soon after the diagnosis because of diabetic coma. The discovery of insulin and then other anti-hyperglycaemic medicines prolonged patients’ lives, but it also gave rise to a number of chronic microvascular and macrovascular complications (Figure 1).<sup>27–29</sup> Recent research confirms that the specific causes of mortality were mainly diabetes-related chronic complications. However, acute complications, especially diabetic ketoacidosis, persisted as an important cause of mortality.<sup>30</sup> In addition, the data from the latest reports indicates an increase in the prevalence of diabetic ketoacidosis at diagnosis of T1DM in Colorado children.<sup>31</sup>

According to the World Health Organization diabetes constitutes the seventh cause of mortality in the 21st century, at the same time being the main cause of blindness, kidney failure and lower limbs amputations.<sup>32</sup>

### 4.4. Diabetic nephropathy

Diabetic nephropathy consists in functional and morphological changes which occur in kidneys and are directly caused by diabetes.<sup>33</sup> At the turn of the 1st and 2nd century of the current era, Claudius Galen described symptoms of diabetes and concluded that they were a result of damaged kidneys, which lost their function of retaining water in the organism.<sup>5</sup> Between 980 and 1037 CE, in his *Canon of Medicine* Avicenna described the urine of diabetic people as ‘heavy, fast-drying and sweet.’<sup>34</sup> The views of Galen that diabetes is a kidney disease were strongly opposed by Paracelsus, who lived in the Middle Ages.<sup>5,35</sup> The first morphological description of pathologies in kidneys of diabetic patients was published in 1895; however, details concerning the lesions became known not until 40 years later.<sup>21</sup> The clinical picture of kidney disease which was described in 1936 by Paul Kimmelstiel and Clifford Wilson with reference to eight patients who died as a result of diabetes was referred to as ‘intercapillary glomerulosclerosis.’<sup>36</sup> They focused on the detrimental effect of disturbed metabolism of carbohydrates on the development of chronic nephrological complications. For decades, structural lesions caused by this problem were addressed as Kimmelstiel-Wilson syndrome. Another renowned pathomorphologist, Paul Ehrlich, was the first to present characteristics of ‘glycogen’ degeneration of renal tubules in the 19th century.<sup>21</sup> In the 20th century, Mogensen proved that increased urine albumin level is a crucial pathogenic factor in kidney damage in diabetic patients<sup>37</sup> and proposed dividing diabetic nephropathy into five stages based on the level of albuminuria or proteinuria. Mogensen also co-authored such terms as ‘incipient (early) diabetic nephropathy’ (manifesting itself as microalbuminuria) and ‘overt diabetic nephropathy’ (manifesting itself as macroalbuminuria – proteinuria).<sup>38</sup> This eminent scholar was first to use the term ‘diabetic kidney disease,’<sup>39</sup> which functioned until 2007, when Kidney Disease Outcomes Quality Initiative (KDOQI) recommended replacing it with the term ‘diabetic nephropathy.’<sup>40</sup>

The currently applied classification of diabetic kidney disease is based on albuminuria and assessment of glomerular filtration rate.<sup>41,42</sup> Because of its imperfections, extensive research is being carried out aiming at finding new biomarkers in the blood or in the urine which could improve diagnosing and prognosticating diabetic kidney disease at its early or later stage.<sup>43</sup> In a few studies, including those conducted in patients with T1DM and DM type 2 (T2DM), it was found that the concentration level of the tumour necrosis factor (TNF) receptors may correlate with the kidney function,<sup>44</sup> although its biological basis remains to be determined.

### 4.5. Diabetic neuropathy

Diabetic neuropathy is the most common complication of diabetes<sup>45</sup>. The symptoms of diabetic neuropathy have been known for a long time. Already in the 11th century Avicenna in his *Canon of Medicine* described symptoms of diabetes and enumerated also two specific chronic complications of

diabetes: gangrene and impotence.<sup>46</sup> The first exhaustive description of the symptoms of diabetic neuropathy was prepared by Rollo at the end of the 18th century.<sup>47</sup> In 1864 Marchal de Calvi, and two years later Ogle confirmed that nerve damage described by Rollo is characteristic of diabetes, while in 1884 Bouchard found no knee jerk in a group of diabetic patients.<sup>48</sup> In turn, a Guy's Hospital doctor Frederick Pavy is the author of a still valid detailed description of diabetic polyneuropathy.<sup>49,50</sup> He observed correlations between diabetes and function disorders of the nervous system, both peripheral and autonomic. The first full definition of diabetic neuropathy was presented at the 1988 San Antonio conference organised by the American Diabetes Association (ADA) and the American Academy of Neurology (AAN). Diabetic neuropathy was described as a disorder of the peripheral nervous system (with manifestations in the somatic and/or autonomic parts) confirmed by the appearance of signs and/or symptoms and/or electrophysiological lesions which appear in diabetic patients after other possible causes were excluded.<sup>51,52</sup> At the same conference, the first typology of diabetic neuropathy was presented, dividing it into non-demonstrable, diffuse and focal neuropathy.<sup>53</sup> In 1993, Watkins presented a classification of diabetic neuropathy based on natural history of disease. The author differentiated a group of symptoms gradually progressing (sensory and autonomic neuropathy) and subsiding (mononeuropathies, radiculopathies and acute painful neuropathies).<sup>54</sup> At annual conferences of the ADA recommendations concerning prevention, diagnosis and treatment of diabetes and its complications are announced.

At present, research is being carried out with the aim of complementing the knowledge on the so far unknown pathophysiological processes leading to the development of diabetic neuropathy. Revolutionary approaches appear, questioning the microvascular hypothesis in the development of early diabetic neuropathy. A new molecular approach has been developing, stating that sensory neurodegeneration is directly caused by diabetes and offering a number of new therapeutic opportunities. Interventions which activate inner pathways leading to regeneration of nerves with the use of such methods as insulin, GLP-1 agonism and the overexpression of heat shock proteins can constitute new strategies of preventing nerve damage or reversing this damage in diabetic neuropathy. Pathogenesis of diabetic neuropathy may encompass epigenetic changes mediated by miRNAs, which regulate gene expression in a number of biological processes, including cell survival and growth. Sensory neurodegeneration in diabetic neuropathy may share its mechanisms with other neurological syndromes, such as anomalies in spliceosomes, deregulation of Cajal bodies and loss of survival motor neurons (SMN) proteins.<sup>55</sup>

#### 4.6. Diabetic eye disease

Although diabetes has been known since 3000 BCE, the issue of eye complications became better known as late as 200 years ago, and first attempts to treat them took place 100 years ago. Eye lesions in diabetic patients were first described

in 1789 by Rollo. Diagnosing damages in the eye caused by diabetes was possible after Helmholtz had constructed the ophthalmoscope in 1884. The first eye pathologies in diabetic patients were described by a Viennese ophthalmologist Eduard von Jaeger in his article 'Beiträge zum Pathologie des Auges' published in 1855. The author termed the newly discovered lesions in the fundus of the eye 'retinitis diabetic'.<sup>56,57</sup> Von Jaeger was also the first scholar to observe what later became known as diabetic macular oedema. However, not all the scientists shared his views then – Albrecht von Graefe negated any correlations between diabetes and lesions observed in the fundus of the eye.<sup>58</sup> Dependencies between diabetes and damages of the macula were undisputedly confirmed in 1969 by Henry Noyes and three years later by Edward Nettleship, who presented research results documenting the presence of histopathological lesions in the maculas of diabetic patients. This way, the researcher laid foundations for the modern definition of diabetic maculopathy.<sup>59,60</sup> The whole current knowledge on lesions in the eye in diabetes was published in 1876 by Wilhelm Manz in a richly illustrated work entitled *Reinitis proliferans*.<sup>61</sup> A year later, using post-mortem research material, Mackenzie was first to describe the presence of microaneurysms in the retina as lesions typical only of diabetes. He also observed bleeding into the retina and the vitreous body in diabetic patients.<sup>61</sup> Nine years later, Nettleship reported a change of shape of retinal veins in diabetic patients and undertook a description of proliferative retinopathy.<sup>62</sup> Natural history of diabetic retinopathy, with division into four types, was presented by Juliusz Hirschverg in 1890, yet the only full description of this condition was published in 1944 by Ballantyne and Lowenstein. These researchers distinguished five stages of diabetic retinopathy, laying foundations for its modern classification.<sup>63,64</sup> In 1954, Lundbeak proposed a term 'diabetic angiopathy' which referred to the disease of small blood vessels caused by diabetes.<sup>65</sup>

At present, we witness a turn in thinking about pathogenesis of diabetic retinopathy – it is no longer seen solely as a microvascular complication; it is perceived now as a neurovascular one.<sup>66</sup> This turn in pathophysiology of retinopathy was initiated by Wolter and Bloodworth's sequence studies, as they discovered degeneration of retinal neurons in diabetic patients.<sup>67</sup> Modern studies confirm that neurodegradation may precede typical vascular damages in diabetic retinopathy. Moreover, diabetic retinopathy develops in patients in various ways and this conditions distinguishing its three phenotypes.<sup>68</sup>

#### 4.7. Macrovascular complications

Macrovascular complications are the cause of death of fifty percent of people with diabetes.<sup>31</sup> In 1987, Krolewski et al. for the first time observed that in T1DM patients ischemic heart disease constituted the main cause of death among people over 30 years of age.<sup>69</sup> The main macrovascular complications of diabetes include the circulatory system diseases, that is: ischemic heart disease, cerebral stroke and lower limb ischemia.<sup>70</sup> Progression of the atherosclerotic process

is the main pathophysiological factor in chronic macrovascular complications. Already in 1973 a hypothesis was formed that there existed a specific vascular disease in the course of diabetes.<sup>71</sup> Then it was proved that cardiovascular diseases in diabetes are caused mainly by premature arteriosclerosis.<sup>72</sup> Numerous studies conducted among diverse populations with various stages of advancement of atherosclerosis have shown that diseases caused by atherosclerosis appear more often in diabetic patients than in non-diabetic patients.<sup>73,74</sup> Hanefeld and Temelkova-Kurktschiev as well as other authors emphasise that the increased progression of atherosclerotic lesions in T2DM patients is primarily caused by after-meal hyperglycaemia.<sup>75,76</sup> In T1DM patients, a decisive factor in this respect might be considerable shifts in the level of glycaemia – from hyper- to hypoglycaemia.<sup>77,78</sup> However, currently a diversified effect of hyperglycaemia on the development of particular cardiovascular complications depending on the age is being put into focus.<sup>79</sup>

The rapidly increasing diabetes morbidity and advancement of its complications have become significant health and social problems whose solution has brought together not only scientists but also politics, due to the increasingly poignant socio-economic consequences of the issue. The first attempt of a systemic regulation of diabetes consisted in the 1989 Saint Vincent Declaration, which determined the basic aims and tasks prerequisite in diminishing individual as well as social burdens of diabetes.<sup>80</sup> This document contributed to considerable improvements when it comes to prevention, diagnosing, treatment, education and rehabilitation in diabetes, yet mainly in developed European countries. As a result of the explosion of the diabetes epidemic all over the world and difficulties reaching the recommended therapeutic aims, despite applying increasingly modern oral antidiabetic medicines and insulin analogues, there is still a strong need to present new strategies of diagnosing and providing therapies when it comes to micro- and macrovascular complications in diabetes.<sup>81,82</sup>

## 5. CONCLUSIONS

Thanks to many years of research and attempts of scientists, at present we can benefit from the knowledge on diagnosing and treating diabetes. However, a significant issue that remains to be addressed is preventing diabetes and stopping the development of its complications, which are a huge interdisciplinary problem affecting all patients. Further research should be undertaken in order to improve the quality of life of diabetic patients as well as providing hope of curing them of diabetes itself and reversing the impact of complications.

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