Celebrating 100 Years of Insulin Use

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Review

CELEBRATING 100 YEARS OF INSULIN USE

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SUMMARY – The year 2022 marked the one-hundredth anniversary of the first application of insulin. November 14th, the birth date of one of its main discoverers, Frederick Banting, was designated as World Diabetes Day. This paper comprises a narrative review of the history of the discovery of diabetes and insulin, progress in insulin development, important breakthroughs in insulin production and delivery, and a short commentary regarding potential future developments in insulin treatment. Diabetes, as one of the earliest recorded illnesses in medical writings, has been a focus of research for almost the entire written human history. Groundbreaking discoveries during the early 20th century have resulted in type 1 diabetes mellitus becoming a treatable, chronic condition. The relationship between good glycemic control and reduced occurrence of diabetes complications was established, which has enticed further development and refinements in insulin treatment, ranging from the purification and increased quality of insulin itself, as well as various inventions in its administration. Despite great achievements in insulin therapy so far, future research aims to avoid the need for subcutaneous administration and to create non-invasive means of insulin application.

Key words: *insulin; diabetes; discovery; type 1 diabetes mellitus; type 2 diabetes mellitus*

Introduction

This year marked the one-hundredth anniversary of the first application of insulin, a drug that has turned type 1 diabetes mellitus (T1D) from a death sentence into a treatable, chronic condition. In addition to its direct therapeutic application, insulin has been of paramount importance in the fields of crystallography, molecular biology, immunology, physiology, and genetics, and the research on insulin has resulted in four separate Nobel prizes. Honoring this centenarian, this paper will review the history of diabetes mellitus, the key findings that resulted in the discovery of insulin and furthered and deepened our knowledge and understanding of insulin in the pathophysiology of diabetes and its application in clinical practice medicine.

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Progress in understanding diabetes

Diabetes as a disease has had a significant impact on human life, and it was recognized and described in the earliest medical texts from different civilizations across the world[1]. The first historical mention of diabetes dates to 1500 BC, when the Hindu Ayurveda

described flies and ants being attracted to the sweet urine of people suffering from a mysterious illness. The term diabetes (meaning "to pass through") originates from 200 AD when it was first used by the Greek physician Aretaeus of Cappadocia to describe a condition of excessive urination. Four hundred years later, sweet urine was associated with polyuria for the first time in Sanskrit literature. An extensive account on diabetes was written around the year 1000 by a Persian polymath Ibn Sina, also known as Avicenna. He went into great length on diabetes, describing issues including gangrene and erectile dysfunction and proposing therapy with a mixture of lupine and other seeds that seems to have a moderate blood-glucose-lowering effect. The first efforts at understanding its causes and pathophysiology were made around the midpoint of the past millennium by a Swiss physician Paracelsus, who discovered an unusual substance in the urine of diabetics that remained as a residue after evaporation. He classified the material as salt and blamed the deposition of this salt in the kidneys for the development of diabetes[1]. For the next 200 years, it was thought that diabetes was a disease that originated from the kidneys. More than a thousand years after the Indians first reported it, in the 17th century, British physician Thomas Willis noted the sweet taste of urine in diabetic patients. He used the Latin term for honey – mellitus – to distinguish this disorder from other causes of frequent urination. He attributed the sweetness, however, to salts and acids rather than sugar[2]. It was not until the 1700s when Matthew Dobson identified glucose in the blood of people with diabetes, which proved diabetes to be a systemic disease. In 1797, Scottish military surgeon John Rollo published a case that detailed the improvement of an officer with diabetes who was put on a meat diet[3]. In a study performed in the late 1790s, he quoted Dobson and created rules for a diabetic diet. Moreover, some credit Rollo instead of Willis for coining the word "mellitus", which he used to distinguish the illness from diabetes insipidus[4]. Decades later, French scientist Claude Bernard discovered that sugar in the urine was stored as glycogen in the liver, which suggested that blood glucose control is influenced by the central nervous system. In 1869, German physiologist Paul Langerhans identified and isolated a cluster of pancreatic cells that were later found to secrete insulin. These clusters were named the islets of Langerhans. Significant medical and technological advances allowed for extensive and methodologic research in this period. The relationship between the pancreas and diabetes was first established in 1889 when Oscar Minkowski and Josef von Mering demonstrated that the removal of the pancreas caused the onset of diabetes in dogs. Until 1920, diabetes was rare and was diagnosed only in children. It was not until 1959 that different types of diabetes were identified, and, since 1960, diabetes has been classified into type 1 and type 2[1]. After the discovery of insulin and the possibility of treating patients with type 1 diabetes, patients began to develop chronic complications of diabetes characteristic of the elderly, such as retinopathy, nephropathy, neuropathy, and cardiovascular disease. It took dozens of years to confirm the link between the development of chronic complications and plasma glucose levels[5].

Discovery of insulin

Ever since diabetes was first described in 1500 BC, physicians and scientists have struggled to find a cure. Without appropriate treatment, the prognosis of affected people was poor. In 1908, German physician George Ludwig Zuelzer successfully produced a preparation from the pancreas that, when injected, prevented blood glucose levels from rising in people with diabetes. Unfortunately, he failed to determine the therapeutic value of his product due to the side effects that followed its administration. Eight years later, the Romanian physician Nicolae Paulescu discovered a hormone released by the pancreas that had a normalizing effect on blood glucose levels which he named pancreine[1]. In 1920, Canadian surgeon Frederick Banting conceived the idea to ligate the pancreatic ducts of a dog and extract and isolate the secretions produced, for potential use as a treatment for diabetes. A year later, he conducted his experiments, assisted by Charles Best and supported by John JR Macleod. Biochemist James Collip subsequently joined the research team to purify the pancreatic extract for clinical testing in humans. Even though in 1923 Banting and Macleod were awarded the Nobel Prize for developing therapeutic insulin, Paulescu wrote to the Nobel Prize committee claiming that he had discovered and used insulin first. His claims were rejected, but his achievements have subsequently been recognized as significant in the history of diabetes. Banting shared the award with Best and Macleod with Collip. In commemoration of this, November 14th, Banting's birthday, was declared World Diabetes Day[6].

Progress in the clinical use of insulin

The first patient who received bovine insulin was a 14-year-old boy Leonard Thompson from Toronto on January 11th, 1922. Upon insulin administration, he recovered and in July 1922, Eli Lilly started manufacturing the first vials of regular insulin, Iletin, which was commercially available in the USA in 1923. The same year, Novo Nordisk started manufacturing insulin in Denmark. At that time, insulin was created by extraction from either the bovine pancreas in which insulin molecule differs from human by three amino acids, or the porcine pancreas in which insulin differs from human by only one amino acid. Due to these differences, 10-55% of patients developed a local allergic reaction due to the creation of antibodies to the noninsulin components of the formulation. The insulin was short-acting, and therefore the patients had to administer insulin up to three times per day to decrease their glucose levels. The first long-acting formulation of insulin, basal protamine-zinc insulin, was synthesized by Hans Christian Hagedorn in 1936[6]. It was applied once daily without the requirement of additional doses of regular insulin. During the fifties, the neutral protamine Hagedorn (NPH) and zinc-insulin (Lente) appeared on the market. In this period, the medical community recognized the requirement for better and more complete glucose regulation, and mixed NPH and regular insulin twice daily became a standard regimen. This same regimen is still in use today[7]. In 1977, a highly purified (single peak) animal insulin was developed, which largely decreased the rates of allergic reactions to insulin and almost eliminated the occurrence of lipodystrophy. Recombinant human insulin was approved for use in the early eighties, synthesized by using recombinant DNA technologies from *Escherichia coli* or yeast[8]. Soon, most pharmaceutical companies switched from using animal-derived insulin to synthetic, recombinant human insulin. Considering the high rates of hypoglycemia in patients using the short-acting regular insulin and intermediate-acting NPH insulin, new insulin analogs were synthesized with minor structural changes in their amino acid sequence, which resulted in significant changes in their action. Short-acting insulin analogs are absorbed and dissociated from the administration site faster than regular insulin, allowing them to better reproduce the physiological secretion of insulin during meals (prandial insulin). Short-acting analogs control the postprandial glucose levels better than human insulin, and they decrease the chance of postprandial hypoglycemia. Lispro, the first short-acting insulin analog, was produced in 1996. Other short-acting insulin analogs include insulin aspart and glulisine[9]. In contrast, long-acting analogs, insulin glargine, degludec, and detemir, have the function of mimicking basal insulin levels in the blood. Due to the hexameric structure, the time of action of these insulins is prolonged, which allows for one administration of long-acting insulin to maintain basal insulin levels in the blood throughout the entire day. When initiating insulin therapy in type 2 diabetic patients, most receive only long-acting, basal insulin, or a combination of basal insulin with metformin or other oral antihyperglycemic drugs. The first basal analog became available for use in the year 2000[9]. The search for an optimal basal analog lasted for years, until 2013, when the first almost ideal basal analog was created, the effect of which lasted more than 24 hours and could accordingly be administered once a day. It has minimal action variability and the lowest risk of hypoglycemia. Today, this progress in mimicking physiological insulin action allows people with diabetes to live a normal life with delayed onset of chronic complications[1].

Biosimilars

Insulin is considered a drug and a biopharmaceutical. Biopharmaceuticals or biologics are medications with active compounds that are produced or secreted by a biological source. Owing to the particularities of their production, the structure of biologics is far more complex than the structure of the active compound of the biological, "original", counterpart. The main downside to biological medications is their high price, resulting in decreased availability[10]. With the development of new insulin analogs, increased accessibility to treatment is expected. However, due to increasing insulin prices, many patients find the treatment too expensive, leaving them without much-needed treatment[11]. A possible solution to make modern insulin analogs more accessible could lie in biosimilars. Biosimilar drugs are medications with quality, biological activity, safety, and mode of action similar to an already approved biopharmaceutical. The relationship between a biosimilar and the original biological drug is akin to the one between generic and original drugs. In generic drugs, the active pharmaceutical is identical to the original, while in biosimilars the active compound does not completely match the original biological

drug. Both generic drugs and biosimilars are produced after the patent license of the original has expired, which enables companies other than the chemical patent owner to produce it, which usually results in a lower market price[10]. Generics are sold at prices 20-90% lower than the price of the originals, which has caused a large increase in their use over the last years, creating large savings[12]. Biosimilars can potentially reduce the overall costs, both due to their lower cost and likewise due to the expected decrease in the price of the original biologic drugs after biosimilars appear on the market[13]. Biosimilar insulins currently approved for use in Europe are Insulin lispro Sanofi, Semglee, Kirsty, Abasaglar, and Insulin aspart Sanofi[14].

Insulin pumps

With the recognition of the role of good glucoregulation in reducing the incidence of diabetes-related complications, strong efforts have been made to find the best physiologic route of insulin delivery. The credit for the first developed insulin pump goes to Arnold Kadish, who invented a closed-loop insulin pump in 1963[15]. Interest in his invention and the subsequent pumps was low, as they were highly impractical due to their size and complexity. Other inventions included continuous intravenous pump infusions developed in the seventies, however, due to risk of complications such as thrombosis, infections, and phlebitis, these devices remained in use mainly for study purposes[15,16]. However, these and other inventions nudged pharmaceutical companies to invest in insulin pump research, which led to the production of the first commercial insulin pumps in the 1980s. These early commercial pumps weighed around 400 grams, required frequent battery changes, were inflexible due to the rigid materials used during their production process, and were often too complex to use, which limited their acceptance among patients and did not result in widespread use[15]. By the 1990s, these technical problems were resolved, and the pumps were safer to use as they alerted the user when they malfunctioned, had longer battery lives, and were overall easier to use[17]. The use of insulin pumps drastically increased after the results of the Diabetes Control and Complication Trials were published in 1993[18]. The results showed a significant reduction in diabetes complication risks in patients with T1D, which far outweighed the increased risk of hypoglycemia[18,19]. Insulin pump use has risen substantially in recent decades. For instance, in the United States, the number of insulin pump users has grown from 7,000 users in 1990 to almost 100,000 users in 2000, and now to over 350,000 users. The vast majority of insulin pump users have T1D, with only 10% having type 2[20]. Over time, many benefits of continuous subcutaneous insulin infusion (CSII) pumps were demonstrated in randomized studies and larger meta-analyses. The use of CSII versus insulin injection therapy offers better glucoregulation, demonstrated by lower HbA1c levels as well as an overall decreased insulin dose[15,21]. With technical advancements, insulin pumps are now the size of a smaller mobile phone, are programmable, and allow accurate dose titration. In addition, they improve the quality of life in patients, but they are correlated with a fear of hypoglycemia, particularly in children[22-25]. Notably, the majority of currently used insulin pumps are open-loop systems, which means the patient still decides the basal daily infusion rate and must calculate the pre-prandial bolus dose. Hybrid closed-loop systems represent the most advanced form of insulin delivery available for people with T1D that offer better glucose control and reduced risk of hypoglycemia. These systems are characterized by the coexistence of algorithm-driven automated insulin delivery combined with manual mealtime boluses[26]. Such closed-loop systems represent a step forward to the development of "artificial pancreases", that will allow even more functionality, flexibility, and spontaneity in daily lives than today.

Inhaled insulin

In addition to subcutaneous therapy, non-invasive insulin is also available. The first such inhaled insulin was produced in 2006 and called Exubera; however, it was withdrawn after a year due to the changes in the lungs that it caused. The next inhaled insulin, Afrezza, was registered in 2015 and is still in use. The target patients for inhaled insulin are those with needle phobia. Many patients are afraid of injections, making it difficult for them to administer the insulin they require and maintain glycemic control. Unfortunately, because Afrezza is simply prandial insulin, in most cases it does not alleviate the aforementioned problem because patients who require basal insulin will still need to inject their basal doses. As a result, while using Afrezza reduces the total number of injections given per day, it does not eliminate injections unless patients exclusively require prandial insulin support[27].

What does the future hold?

As the prevalence and incidence of people suffering from diabetes rise, it has become increasingly vital to strive toward a safe, effective, simple, and economical solution to the problem of achieving glycemic control. Even though insulin therapy was introduced 100 years ago, the research and development of insulin are still ongoing. Future insulin therapy is likely to consist of once-weekly insulin doses; however, additional advancements in insulin technology, such as hepato-preferential, oral, glucose-responsive ("smart insulin"), and cardioprotective insulins will take considerably longer to become conventional treatment. However, no insulin, no matter how effective it may be, cannot be as "smart" as to think for its users and correct their errors in the fundamental principles of diabetes care. Therefore, people with diabetes should act as partners and assistants to diabetologists in the treatment of their disease.

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Sažetak

OBILJEŽAVANJE STOTE GODIŠNJICE PRVE PRIMJENE INZULINA

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Godine 2022. obilježena je stota godišnjica prve primjene inzulina. Četrnaesti studenog, datum rođenja Fredericka Bantinga, jednog od izumitelja inzulina, proglašen je Svjetskim danom dijabetesa. U ovom radu pružamo narativni pregled povijesti otkrića šećerne bolesti i inzulina, napretka u razvoju inzulina, važnih otkrića u proizvodnji i isporuci inzulina te kratak komentar o potencijalnom budućem razvoju u inzulinskoj terapiji. Šećerna bolest, kao jedna od najranijih zabilježenih bolesti u medicinskim spisima, bila je tema istraživanja tijekom gotovo cijele pisane ljudske povijesti. Revolucionarna otkrića ranog 20. stoljeća dovela su do toga da šećerna bolest tip 1 postane lječivo, kronično stanje. Kada je utvrđen odnos između dobre kontrole glikemije i smanjene pojave komplikacija šećerne bolesti, potaknuti su daljnji razvoj i usavršavanje inzulinske terapije, uključujući pročišćavanje i unapređenje kvalitete samog inzulina, kao i razne izume u njegovoj primjeni. Unatoč velikim postignućima u inzulinskoj terapiji do sada, budućim istraživanjima cilj je izbjeći potrebu za potkožnom primjenom i stvoriti neinvazivne načine primjene inzulina.

Ključne riječi: *inzulin, šećerna bolest, otkriće, šećerna bolest tip 1, šećerna bolest tip 2*