Review Article

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Challenge of diabetes mellitus and researchers' contributions to its control

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Abstract: The aim of this review study was to assess the past significant events on diabetes mellitus, transformations that took place over the years in the medical records of treatment, countries involved, and the researchers who brought about the revolutions. This study used the content analysis to report the existence of diabetes mellitus and the treatments provided by researchers to control it. The focus was mainly on three main types of diabetes (type 1, type 2, and type 3 diabetes). Ethical consideration has also helped to boost diabetic studies globally. The research has a history path from pharmaceuticals of organic-based drugs to metal-based drugs with their nanoparticles in addition to the impacts of nanomedicine, biosensors, and telemedicine. Ongoing and future studies in alternative medicine such as vanadium nanoparticles (metal nanoparticles) are promising.

Keywords: antidiabetic drugs, insulin-mimetic agents, animal models, biosensors, vanadium nanoparticles

1 Introduction

There are many diseases that affect the health of human beings. Some referred to as communicable diseases are infections from microorganisms (bacteria, fungi, and viruses), which spread through contact. In other cases, noncommunicable diseases such as Alzheimer's disease, asthma, heart diseases, and diabetes mellitus could be inherited but not through contact. Diabetes mellitus, simply, "diabetes," is referred to as a global disease. It is caused by a disorder in food metabolism in the human and mammals because of abnormal secretion of insulin

from the beta cells in the pancreas [1]. The outcome is either high blood level/high glucose level (that is hyperglycemia) [1–6] or low blood level/high glucose level (that is hypoglycemia) [7,8]. Complications arising from high and low glucose levels when not treated lead to atherosclerosis, ocular disorder, diabetic retinopathy, cardiac abnormalities, cardiovascular diseases, renal dysfunction, and other diseases of the blood vessels [9–11]. Medications are failing with side effects, and there is the likelihood of more widespread diabetes this coming decade because of urbanization, growing and aging states of people, and increasing childhood and adult obesities [12–15]. The present statistics of diabetic patients is alarming with the prediction of higher subjects. World Health Organization (WHO) gave an estimate of about 171 million in the world that had diabetes in the year 2000 to 366 million by 2030 [16]. International Diabetes Federation's (IDF) Diabetes Atlas also gave an estimate of 578 million adults as diabetic patients in 2030 and 700 million in 1945 [17]. This increase is believed to be primarily due to the global population aging, a decrease in exercise, and increasing rates of obesity [18,19]. Lasker et al. predicted that by the year 2025, 334 million (6.3%) of the global population will have diabetes [1]. The five countries with the greatest number of people with diabetes as of the year 2000 were India having 31.7 million, China 20.8 million, the United States 17.7 million, Indonesia 8.4 million, and Japan 6.8 million [16,20]. World Health Organization (WHO) recognized it as a global epidemic disease [21]. The chart in Figure 1 shows the number of diabetes sorted by age globally in 2017 and a predicted number also sorted by age groups in 2045 [15]. The curiosity was, "Why was there high statistics with over the years treatment?" In essence, aging population, western lifestyle, lack of exercise, obesity, drawbacks, and side effects due to surgery and use of drugs had led to the high statistics of diabetic patients [22]. In sub-Saharan Africa (SSA), diabetes mellitus affected 15.9 million people in 2017 and is predicted to increase to 40.7 million people by 2045 [23]. At the close of 2000, 1.7 million Africans were reported to be diabetic patients, with a predicted increase to 18.6 million in 2030 [24].

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Figure 1: Worldwide prevalence and prediction of diabetes in 2017 and 2045 [15].

At the continental level, the top five countries with the highest number of people affected by diabetes in SSA are about 1.2 million Nigerians, 841,000 South Africans, 552,000 Congolese, 550,000 Ethiopians, and 380,000 Tanzanians [25]. In terms of medical attention, the top five countries with the highest costs of diabetes' treatment are South Africa, Kenya, Zimbabwe, Nigeria, and Ghana [23–25]. The American Diabetes Association (ADA) and WHO were able to classify diabetes into type 1 (autoimmune and non-autoimmune, with beta-cell damage), type 2 (various degrees of insulin hyposecretion and insulin resistance), GDM and other types such as endocrinopathy [26,27]. The terminologies such as “insulin-dependent diabetes” and “noninsulin-dependent diabetes” were no longer used to describe the main groups of diabetic patients. Currently, terminologies such as “type 1 diabetes” and “type 2 diabetes” are used to define diabetes. Diabetic patients, more than half of the world population, are from developing countries, including South Africa [28]. It was said that one of every five South African older than 35 years had the possibility of having type 2 diabetes (T2D), and 50% of this age group is not aware that they have it [29]. This study aimed at the history of diabetes and researchers' contributions to control the disease.

2 Methodology

The methodological approach of this study included a historical review of diabetes from Before Common Era (B.C.E.) to the contemporary period.

2.1 Methodological approach

Content analyses that discussed history and medical records on diabetes were assessed.

2.1.1 Chronological antecedents and medical records of diabetes

The literary version of diabetes is to drain off or siphon fluids from diabetic patients than the quantity they consumed [1]. Historic events of diabetes can be dated back to 3,500 years ago in Egypt [1,30–32]. In 1552 B.C.E., Hesy-Ra, an Egyptian physician, recognized that people with recurrent urination that resulted in weight loss might have diabetes [33]. Primordial healers also observed that ants were drawn to the urine of diabetic patients [34]. Hesy-Ra and other Egyptian physicians researched to develop treatment for diabetes. This persuaded diabetic researchers in other border countries like Arab, Asia, and ancient Greece [1]. About 250 B.C.E., the Greeks explained that the disease dissolved flesh and limbs into urine [1]. Ionian Greek, Apollonius of Memphis could have named the disease, “diabetes,” but in the same era, he and his co-workers studied diabetes as a disease of the kidney where they suggested bloodletting and dehydration as mere remedies [35]. Between 30 B.C.E. and 50 C.E., Aulus Cornelius Celsus gave the maiden description of diabetes [36]. In the second century, ancient Greek physicians, named Aretaeus of Capadocia and Galen, who were supporters of Hippocrates, made efforts in coining the name “diabetes” [1,31,34]. After the name was coined, a series of events followed. Between the fifth and sixth century C.E., apart from the discovery of gestational diabetes, two Indian physicians, Susruta and Charata, were able to differentiate between the two main types of diabetes, namely, type 1 and type 2 diabetes [32,37]. They also described that the urine of diabetic patients is sweet and sticky, which attracted ants. Then, in the seventh century C.E., two physicians, a Chinese Chen Chuan and a Japanese Li Hsuan, described the sweetness of urine of diabetic patients and also found that it attracted dogs [37]. They further said, “diabetics are susceptible to boils and lung contagion, whereby they suggested abstinence from intimacy and wine as solutions for the treatment of diabetes mellitus”. Between 9th–11th centuries, Avicenna (Ibn-Sina) gave an exact description of diabetes [38]. In addition, he said, “gangrene and fall down of sexual dysfunction were precise complications of diabetes” [1,37]. He suggested a mixture of fenugreek, lupin, and zedoary seeds as the treatment for the minor hypoglycemic activity [1]. In 1675, a British called Thomas Willis added the word, “mellitus,” meaning honey sweet after he found again the sweetness of urine and blood in ancient Indian diabetic patients [39]. He published his findings in his book called, *Pharmaceutice Rationalis*. Willis's research prompted a novel

study in diabetic studies in the United Kingdom [34]. Seven years after, Johann Brunner experimented on a dog to observe the importance of the pancreas in the pathogenesis of diabetes mellitus although he did not ascertain the exact organ [33,40]. A year after, Matthew Dobson, also a British, recognized the occurrence of surplus sugar in urine and blood due to their sweetness. Nine years later, William Buchan gave a stress description of dehydration, frothy saliva, thirst, and elevated body temperature experienced by diabetic patients [33]. In 1788, Cowley conducted the first autopsy on diabetic patients with his discoveries reported in *London Journal of Medicine* [33]. Between 1797 and 1809, a Scottish physician called John Rollo pioneered medical therapy to cure diabetes mellitus [1,41]. His prescription was based on the control of the disease with an animal diet, consisting of “normal blood puddings” and “fat and rotten meat” [42].

2.1.2 Contemporary period

In the modern era, historical antecedents of diabetes concurred with the occurrence of investigational medicine [37]. In 1815, Michel Eugene named sugar in the blood and urine as glucose [43]. In 1857, French Claude Bernard established the importance of the liver in glycogenesis [44]. Fourteen years after, a German medical student called Paul Langerhans found the islet cells of the pancreas; however, he could not describe the function [1]. Apollinaire Bouchardat, a physician from France in 1871, observed the loss of glycosuria in diabetic patients when the food was rationed during the Franco-Prussian War in the Siege of Paris. He made modified diets to treat the illness [45]. In 1889, two French scientists, Oskar Minkowski and Joseph von Mering of the University of Strasbourg, proved that the elimination of a dog's pancreas ensued diabetes [34]. In 1901, Eugene Opie, a pathologist at John Hopkins University in Baltimore, Maryland, instituted a link between the failure of the islet of Langerhans in the pancreas and the occurrence of diabetes mellitus [46]. Nine years after, Sir Edward Albert Sharpey-Schafer, an English physiologist, discovered insulin [40]. It derived its name from a Latin name, “insula,” which means island [37,40]. This refers to insulin-producing islets of Langerhans in the pancreas [40]. John J. R. Macleod wrote a book on diabetes entitled, *Diabetes: Its Pathological Physiology* in 1913 [40]. Another author, Elliot Joslin, a Boston pathologist, brought together a thousand of his cases and wrote the textbook, *The Treatment of Diabetes* in 1916 [47]. In his textbook, he stressed the importance

of fasting and consistent exercise as a treatment for diabetes. This book and his further research gave him a reputation as a renowned expert in diabetes in 1916 [47]. To control the disease of diabetes, Frederick Allen from Rockefeller Institute in New York in 1919 printed his write-up, “Total Dietary Regulations in the Treatment of Diabetes,” which was based on the treatment of strict dieting. Banting's research made him to discover insulin in July 1921 [47]. The extract worked upon Dog 410 in Professor J.J.R. Macleod's laboratory space in the University of Toronto in August 1921 [40]. Frederick Banting and Charles Best found that the extract of fetal pancreas from bovine reduced the blood glucose level when used on depancreatized dogs [48]. The extract served as a guide to produce abundant low-priced insulin in November 1921 [40]. The purification of extracts was done to improve the quality by James Bertram Collip, Frederick Banting, and Charles Best in November 1921 [40]. The treatment of diabetes using insulin was administered on Leonard Thompson, a volunteer, in January 1922, while insulin was first mentioned publicly in May 1922 [40]. The mass production of insulin was done with the collaboration of the University of Toronto and Eli Lilly & Co of Indianapolis [72]. In August 1922, Banting administered insulin on diabetic Elizabeth Evans Hughes, where she responded to healing through insulin [49]. The contributions of the four scientists were recognized in the discovery of insulin, but only Banting and Macleod were awarded 1923 Nobel Prize in Physiology or Medicine [40]. This same year, October 1923, insulin became marketable in the United States and Canada. Dr Priscilla White set up the Joslin Pregnancy Clinic from her experience of half of the babies who survived from diabetic mothers in 1924 [40]. Originally when delivering insulin, big and weighty reusable syringes were used. Boiling was used to sterilize these syringes to safeguard effective reuse [50]. In 1924, Becton Dickinson (BD) produced the first syringe specifically for insulin injection, while in 1925, Novo Nordisk launched its first insulin syringe called the “Novo Syringe” [50]. In 1926, Abel prepared the first chemical structure for insulin [1,40]. The two-dimensional chemical structure of insulin is shown in Figure 2 [51].

In 1928, insulin was described to be a protein made up of amino acids [1]. Insulin has a molecular mass of 5831.648 g/mol with a chemical formula of $C_{256}H_{387}N_{65}O_{79}S_6$ [52]. In 1936, Hans Christian Hagedorn founded Novo Nordisk and ascertained that the addition of protamine to insulin extended the period in which the drug acted [53]. As a result of the increase in the number of diabetic patients and the complications they experienced,

Figure 2: The two-dimensional chemical structure of insulin [51].

American Diabetic Association (ADA) was founded in 1940 [54]. In 1942, Janbon discovered sulfonylurea as the first oral hypoglycemic agent [1]. Rachmiel Levine, a medical doctor by profession, and colleagues discovered in 1949 that insulin is responsible for transporting glucose into cells [55]. The same year, BD and Company produced a standardized insulin syringe which was endorsed by ADA [56]. In 1952, the ADA funded its first research grants in diabetes [57]. A year after, tablets for testing urine glucose and urine test strips were introduced and were commonly available [37]. In 1954, American Dietetic Association in collaboration with the United States Public Health Service formulated a meal planner, which divided foods into six groups based on calories, carbohydrates, protein, and fat in each served food [58]. In 1955, Franke and Fuchs discovered sulfonylureas hypoglycemic agents (tolbutamide and carbutamide), which were administered orally and were sold for the first

time [59]. In 1959, two researchers, named Solomon Berson and Rosalyn Yalow, devised a method using the radioimmunoassay technology to measure insulin in the blood [60]. Both recognized type 1 diabetes as insulin-dependent diabetes and T2D as noninsulin-dependent diabetes. Barely, 24 months after, Eli Lilly and Company introduced a hormone called glucagon, which was produced by the pancreas to increase glucose levels to treat severe low blood sugar levels (hypoglycemia) [61]. In 1964, Anton Hubert Clemens Company called “Ames Company” launched the first strips for testing blood glucose using color code [62]. A condition characterized by high blood glucose levels is caused by either a lack of insulin or the body’s inability to use insulin efficiently. Type 2 diabetes develops most often in middle-aged and older adults but can also appear in young people. Pancreas transplantation was carried out for the first time at the University of Manitoba Hospital in 1966 [63].

Subsequently, Ames Company launched the first handy glucose meter called Ames Reflectance Meter in 1970 [63,64]. In 1971, Pierre Freychet made known insulin receptors on cell membranes [55]. A year later, U100 insulin was introduced [34,40]. The introduction of U100 into marked U100 scale insulin syringes decreases the frequency of dosing errors. [65]. In 1974, Biostator was launched to allow continuous glucose monitoring and closed-loop insulin infusion [66,67]. In the same year, human leukocyte antigens were developed on cell surfaces [68]. Two years later, the first insulin pumps were invented to treat type 1 diabetes [50,69]. In 1977, Rosalyn Yalow's work was based on the measurement of insulin in the body, which fetched her Nobel Prize in Physiology and Medicine [70]. The same year, researchers in Boston developed a blood test called the A1C test to measure a person's average blood glucose [71]. In 1978, researchers in City of Hope National Medical Center in Duarte, California, and Genentech, Inc., in San Francisco, California, used a form of the human insulin gene and introduced it in *Escherichia coli* to produce synthetic human insulin, which was identical to human insulin [72]. In diabetic patients, portable insulin pumps were introduced and used to obtain normal blood glucose levels [73]. Today, the size made it a disadvantage. The same year, Federal Government established the National Diabetes Information Clearing House to collect and document all diabetic literature [74]. In 1979, National Diabetes Data Group introduced new classification systems: (i) type 1 diabetes (insulin dependent), (ii) T2D (noninsulin dependent), (iii) gestational diabetes, and (iv) diabetes associated with other syndromes or conditions [74].

2.1.2.1 Type 1, type 2, and type 3 diabetes with their animal models

Animal models have immensely contributed to the study of diabetes mellitus, where researchers are privileged to control the genetic and environmental factors that may have an impact on the disease development and establishment of complications with *in vivo* tests [75–77]. As a result, researchers gain new information about its handling and treatment in humans. Animal models develop diabetes either freely or by using chemical, genetic, surgical, or other methods and show many clinical features or relevant disease phenotypes [75,76]. In addition, an animal model for biomedical research is a normative life science or action that can be studied by investigating the spontaneous or induced pathological process, and in which the occurrence in one or more regards looks like

the same occurrence in humans or other animal species [78,79]. An innovative animal model of type 1 diabetes called the nonobese diabetic mouse strain was described in 1980 [77,80,81]. Initiation of the concept of basal-bolus, otherwise known as intensive insulin therapy, is used in clinics to treat patients with type 1 diabetes efficiently. Basal-bolus therapy is the first-line treatment given to type 1 diabetic subjects after the Diabetes Control and Complications Trial (DCCT) [82,83]. It involves self-administration of insulin based on regular home blood glucose monitoring (HBGM) [82,83]. In the case of T2D, TALLYHO/Jng mouse is used as an inherited polygenic model with tolerable obesity [84]. Another generally used model for T2D is the high fat-fed C57BL/6 mouse, which shows various types of features of the diabetic phenotype usually found in obese humans, including insulin resistance and hyperinsulinemia [85,86]. Nevertheless, the diet-induced obese mouse does not reveal glucose-mediated insulin secretion, which is typical of human type 2 diabetic subject, and show expansion of beta-cell mass like db/db and ob/ob mice [87,88].

Gestational diabetes (GDM) is glucose predisposition that develops or is first observed during pregnancy. There are inadequate treatment options for GDM [89]. It is otherwise known as type 3 diabetes. To enhance treatments and understand the mechanisms, suitable GDM animal models are essential [90,91]. In addition, various parts of human diabetic pregnancies, such as amplified spontaneous abortion rates, fetoplacental deficiencies, malformation, and descendants diseases in future life can be approached using suitable animal models [92]. Some researchers used C57BL/6J female mice as a GDM model [93]. Their findings revealed that GDM induces additional maternity weight gain and fetus weight, with irregular material circulating metabolic and inflammation matters and forms a placental hypoxia eco-friendly and influences the placental vascular development [94,95]. The outcome is the likelihood of high threats of perinatal complications of obesity in GDM mothers. Aziz et al. used female Sprague–Dawley rats as the GDM animal models [91]. Results from their findings showed the disease imitation in humans, which can serve as a reference for future study. With the similar result, but different animal models, Kiss et al. used female Wistar rats for the GDM animal model [96].

2.1.2.2 Animal model assessment

There must be an animal model assessment based on relevant species because of the various animal models

developed to imitate human disease conditions [97]. Animal risk should be reduced to obtain the best model for both lawful and ethical obligations [98,99]. Ethical principles could assist to fill the gap between increasing the disease knowledge and the increasing disease incidence [100]. Russell and Burch suggested that the use of animals as models must stick to the three “Rs:” (i) replacement (exchanging animals with nonanimal (substitute) models), (ii) reduction (decreasing the number of animals for research), and (iii) refinement (embracing the best quality care for the animal) [101,102]. Food and Drug Administration (FDA) endorsed the induced human insulin produced from genetically human insulin [72]. In 1982, Eli Lilly used the recombinant DNA technology to build up Humulin, a new biosynthetic human insulin, which is the same as human insulin [103]. It can undergo mass production [104]. In addition, a 64K, an autoantibody was discovered and found to be linked with type 1 diabetes [105]. In 1983, low blood sugar's association with brain metabolism was recognized [106]. Second-generation sulfonylureas became launched in the market, allowing patients to administer small doses with fewer side effects in 1983 [107,108]. A year later, insulin molecule was recognized to be the target of the autoimmune response in type 1 diabetic patients [109,110]. Scientists were able to connect pregnancy with aggravating cases of diabetic retinopathy in 1985 [111]. Twelve months later, a report from The National Diabetes Data Group showed that T2D was more prevalent among African Americans, Mexican Americans, and Native Americans than it can be found among Caucasians [112,113]. Reports further said that 50% of all Pima Indians in Arizona who were older than 35 years had diabetes – highest population worldwide in 1986 [114]. The 64K, which was first discovered in 1982, was predicted to be type 1 diabetes in 1987 [37,115]. In addition, researchers studied that proper control of glucose levels during pregnancy is essential for the health of the fetus [116]. They continued to research on how diabetes aggravates birth defects. In 1989, ADA publicized its first standards of care I order to guide physicians in treating diabetes [117,118]. The study also revealed how a transporter, called GLUT-4, distributes glucose to muscles and fat cells [119]. In 1990, an essential enzyme and a protein called glutamate dicarboxylate (GAD) was found to be involved in cellular communication in the brain and the pancreas [120]. The attack of the immune system on GAD activates a quick autoimmune response that causes diabetes [121,122]. In 1993, DCCT confirmed that good maintenance of blood glucose levels controls eye, kidney, and nerve diseases caused by problems arising from complications from diabetes after a ten-year clinical study

[123]. A year later, FDA endorsed Captopril to treat end-stage renal disease [124,125]. Leptin, a fat cell hormone, that modulates attitudes of feeding and secreting hormone was cloned [126,127]. A survival study called “Scandinavian Simvastatin Survival Study” (4S) confirmed that reducing the cholesterol with statins will decrease the risk of myocardial infarction or stroke, whose impact could be much felt among diabetic patients [129]. In the mid-1990, incretin hormone glucagon-like peptide-1 (GLP-1) was found. It helps to promote the production of insulin when it is secreted in response to food [130]. The GLP-1 led to the introduction of diabetic drugs that could enhance insulin secretion in response to glucose and also enhance the number of beta cells in the pancreas [131]. Metformin is a biguanide, which prevents the production of glucose in the liver (Figure 3) [132,133]. Metformin has a molecular mass of 129.163 g/mol with a chemical formula of $C_4H_{11}N_5$ [134]. The trade name is “Glucophage,” and it became available in United States in 1995 [135].

The following year, acarbose, an alpha-glucosidase inhibitor, under the brand name “Precose,” which became available in United States, helped for slow digestion of some carbohydrates. Eli Lilly and Company introduced the longest-acting insulin, Lispro (Humalog), as the first human synthetic insulin in 1996 [53]. Insulin lispro and insulin glargine (toujeo) are optional valid treatments but do not work like natural insulin because they take a longer duration to absorb due to clumping when injected [137]. They are lysine–proline analog. In 1997, FDA endorsed another antidiabetic drug called troglitazone (Figure 4) [138]. Troglitazone has a molecular mass of 441.541 g/mol with a chemical formula of $C_{24}H_{27}NO_5S$. Its brand name is Rezulin (Park–Davis). [139]. It belongs to thiazolidinediones that enhances insulin sensitivity in muscle cells. The drawback of liver toxicity made it to be banned from sale [138]. It had been replaced with rosiglitazone and pioglitazone.

In 1997, Richard Bernstein published a book called, *Diabetes Solution*, which dealt with reducing the consumption of carbohydrates to get excellent blood glucose and prevent diabetic-related complications [140]. Meanwhile, the fasting glucose level used to diagnose diabetes was reduced from 140 to 126 mg/dL [141]. In 1998, Novo Nordisk produced Repaglinide belonging to the class of drugs called meglitinides (Figure 5) [142]. It has a

Figure 3: The chemical structure of metformin.

Figure 4: The chemical structure of troglitazone.

molecular mass of 452.586 g/mol and a chemical formula of $C_{27}H_{36}N_2$. The brand name is Prandin. It stimulates the secretion of insulin in the presence of glucose [143].

The United Kingdom Prospective Diabetes Study (UKPDS) confirmed that diabetic patients who control glucose levels and blood pressure reduce complications due to T2D [144]. Similar results were obtained from DCCT in type 1 diabetic patients [145,146]. There were transformations in diabetes around the world from these two studies. At the University of Alberta, scientists accomplished the pioneer islet transplant in 1999 [147]. The following year, Shapiro et al. published their results from a research carried out on seven patients with type 1 diabetes who went through the procedure to achieve insulin independence [148,149]. Many first-year patients of type 1 diabetes treated with anticluster of immunology 3 (anti-CD3) monoclonal antibody, hoKT3gamma1 (Ala-Ala), had enhanced metabolic control and insulin production in 2002 [150]. The same year, ADA defined prediabetes as impaired fasting glucose (IFG) of 100–125 mg/dL or impaired glucose tolerance (IGT) of 140–199 mg/dL [151]. Both processes included base consumption of glucose-rich drink after 2 h. Three years after, a first-in-class incretin mimetic (GLP-1) drug known as exenatide (brand name Byetta) was endorsed in the United States to treat T2D [152]. It is an injectable drug that helps to increase insulin production in response to blood sugar levels (BGLs) [153]. Another injectable adjunct drug, Pramlintide (brand name, Symlim), was endorsed in the United States to treat people who administer insulin during meal times, but the blood glucose levels still remained same [154]. Sitagliptin, which was formerly known as MK-0431, was sold as the phosphate salt with the trade name Januvia in the United States (Figure 6) [155]. The molar mass is

Figure 5: The chemical structure of repaginate.

407.316 g/mol, and the molecular formula is $C_{16}H_{15}F_6N_5O$. It was introduced and sold by Merck and Company. It is an oral antidiabetic drug of dipeptidyl peptidase-4 (DPP-4) inhibitor used to treat T2D [156]. The enzyme-inhibiting agent could be used as a single therapy or a combination therapy (with metformin or thiazolidinediones) [157]. The DPP-4 is an enzyme that naturally obstructs incretin GLP-1 and GIP gastrointestinal hormones by inactivation because GLP-1 works in the gut to enhance insulin secretion [156]. It was introduced and sold by Merck and Company. The US FDA endorsed sitagliptin as the first drug in the class of drugs called DPP-4 inhibitors on October 17, 2006 [158]. They boost the body's capability to reduce blood sugar [159].

The FDA also endorsed an oral combination of sitagliptin and metformin, which was marketed in the United States as Janumet on April 2, 2007 [160]. In 2008, three studies, namely, ACCORD, ADVANCE, and VADT had the results published and presented at ADA Scientific Sessions [161]. The results were disadvantageous to promote thorough glycemic control on outcomes from high cardiovascular risk experienced in patients with T2D [162]. In the same year, Suzanna M de Monte suggested type 3 diabetes to illustrate insulin resistance in the brain [163]. Subsequently, in 2009, A1C levels of 5.7 to 6.4% were used to verify people with prediabetes [164]. In the United States, FDA endorsed another oral combination of sitagliptin and simvastatin sold as Juvisync on October 7, 2011 [165]. Simvastatin has a molar mass is 418.566 g/mol, and the molecular formula is $C_{25}H_{38}O_5$ (Figure 7).

The first in the class of SGLT-2 inhibitors is called canagliflozin (Figure 8), with a molar mass of 444.52 g/mol, and the molecular formula is $C_{29}H_{25}FO_5S$ [166]. The trade names of canagliflozin are Invokana, Prominad, and Suli-sent, with the FDA endorsement in 2013 [167,168]. In the same year, the University of Cambridge tested an artificial pancreas, which was a combination of an insulin pump with a continuous glucose monitor [169–171]. In 2015, Edward Damiano introduced iLet, which is a bionic pancreas that

Figure 6: The chemical structure of sitagliptin.

Figure 7: The chemical structure of simvastatin.

Figure 8: The chemical structure of Canagliflozin.

distributes both insulin and glucagon every 300 s [40]. He described the appliance as a, “bridge to a cure.”

Ethical approval: The conducted research is not related to either human or animal use.

3 Nanotechnology

In the 21st century, a recent concept is the application of nanotechnology to medicine [172]. It has several advantages such as improved glucose sensor technology with abilities of more numerous and appropriate blood glucose measurements [173–175]. Nanomedicine is navigating the progress of medical and pharmaceutical sciences to several nanoformulations and drug delivery systems [176]. Nanotechnology uses nanoscale influence to improve the *in vivo* delivery systems of therapeutic agents [177]. Numerous nanodrug delivery systems have been explored to orally deliver hypoglycemic agents such as lipid nanoparticles, liposomes, micelles, nanoemulsions, and classes of polymeric nanoparticles [178,179]. There is the supremacy of nanodrugs to conventional therapy in terms of availability, drug doses, drug side effects, target tissue selectivity, and purity [176,180].

3.1 Nanomedicine and diabetes mellitus

A recent development in nanotechnology-based methods embraces a significant possibility for improving the care of diabetic patients [181]. The clinical application of these technologies will enable diabetics to manage the disease more efficiently and improve their health and quality of life [182,183]. The nanotechnology research in diabetic

management entails islet implantation, insulin and drug discovery, glucose monitoring, and diagnostic approaches [174,184].

3.2 Nanomedicine and type 1 diabetes treatment

Human islets transplantation of an undamaged pancreas could cure diabetes, provided they are cases with synchronized kidney transplantation, where immunosuppression is previously essential [185]. Current developments in cell reprogramming and beta-cell differentiation permit the individualized stem cell generation to give a limitless source of beta cells for research and to develop autologous cell therapies [186,187]. However, there are challenges to develop beta cell replacement therapies [188]. These challenges incorporate suitable quality controls of the stem cells being used, the capability to produce beta cell implantations of firm cellular configuration, and in type 1 diabetes cases, to protect implanted cells from autoimmune derelict without affecting the immune system, other aspects, or the implantation functionality [189]. These new treatments should match or surpass the comparative safety and efficiency for available diabetes care [187,189,190]. Two groups of researchers stated some other treatments, such as boxes with nanopores that protect transplanted beta cells from the immune system attack, nanoparticles, or nanospheres as biodegradable polymer carriers for oral delivery of insulin, as well as synthetic pancreas and synthetic beta cell as substitutes for oral delivery of insulin [189,191]. Nanomedicine has also supported stronger delivery systems that can detect variations in BGLs and automatically control the insulin release rate in type 1 diabetes to sustain normoglycemia [192]. For helping early type 1 diabetic diagnosis, developed nanoparticles are used as imaging contrast agents [174]. The method entails merging glucose nanosensors in implantable devices, which allow more exact and patient-friendly actual-time tracing of blood glucose levels, and also provides the source for glucose responsive, which acts better to imitate the body's physiological requirements for insulin [174]. They also used nanotechnology in noninvasive methods for insulin delivery and bring about more efficient cell, gene, and vaccine therapies for type 1 diabetes. A group of researchers were not only of the opinion of the implantable nanosensors but also stated the use of microphysiometer and nanopump [192]. Microphysiometer is a structure made of multiwalled electrically conductive carbon nanotubes, which are like numerous flat sheets

of carbon atoms arranged and moved into very small tubes to detect periodic functional responses from living cells as well as provide new information on cell signaling, which is often unavailable from other assay methods [193]. The nanotubes work steadily at body pH levels [194]. Nanopump is a basic device that has countless applications in medicine [195]. Current detection approaches entail insulin production measurement at intervals by collecting small samples and assessing their insulin levels period by period [196]. This new approach entails detecting insulin levels boundlessly by measuring electron transfer formed when insulin molecules oxidize in the presence of glucose [197,198]. When electrons are formed, there will be an increase in the sensor current and *vice versa*, permitting monitoring insulin concentration in actual time [198].

3.3 Nanomedicine and T2D treatment

It had been reported that insulin can treat T2D with its intracellular activity, but insulin intracellular delivery is a challenge in basic research or clinical medicine [198,199]. In drug delivery, nanotechnology supports drugs that have experienced poor bioavailability challenges or that caused adverse outcomes when delivered via conventional forms [184]. A model delivery vector with effective internalization and high stability should be able to overcome this challenge [200]. Xiao et al. stated that a biomineralization modification of insulin can deliver it into whole cells on a large scale, resulting in long-term therapeutic actions on diabetic mellitus [200]. Recently, several nanomaterials such as liposomes, micellar formulations, nanocages, nanotubes, polymer drug conjugates, and polymeric nanoparticles were used as intracellular insulin (protein) delivery carriers [201]. This gives a new approach to biomimetic nanotechnology for biomedical applications [202].

3.4 Nanomedicine and type three diabetes treatment

Currently, in the medical diagnostic method for GDM therapeutics, there is a challenge to deliver and secure drugs to the accurate position [203]. As a result, Cheng et al.'s research focused on the green synthesis of gold nanoparticles (Au-NPs) by means of *Ramulus mori* leaf extract with methanol in an environmentally friendly approach. Methanolic leaf extract, gold(III) chloride, and polyacrylic acid were used to synthesize polyacrylic

acid gold nanoparticles (Au-PAA-Nps) via the process of institute chemical polymerization [203]. They used rat (*in vivo* screening) to assess the drug delivery system and concluded that Au-NPs were active against gestational diabetes, as a new approach to treat GDM. Other antidiabetic delivery drugs are anionic liposomes including (cholesterol, DPPC, DSPEPG8G, and DPPG for GLP-1) liposome-based system (glycerolphosphate-chitosan microcomplexation for metformin), niosome-based system (cholesterol, span 40, and span 40/cholesterol dicetyl phosphate for metformin; DOTAP for metformin hydrochloride; cholesterol for repaglinide; cholesterol and span 20 for pioglitazone; cholesterol for gliclazide; and span 60), and polymeric nanoparticles-based system (for repaglinide) [204–207].

3.5 Safety of nanomedicine to diabetes treatment

Nanomedicine entails the use nanoparticles for therapeutics and diagnosis in diabetes treatment [172]. Present-day nanotherapeutics such as Abraxane and Doxil show some side effects, while other nanoparticles (metallic and carbon-based particles) are likely to show toxicity [174]. Significantly to be mentioned is the safety of these nanoparticles for biocompatibility and desired activity to be attained [208]. Wolfram et al. reported the use of surface modification and pretreatment with immunomodulators as strategies to improve nanoparticles' safety [208].

4 Recent developments, biosensors, and telemedicine (TM)

4.1 Biosensors

To improve the management of diabetes mellitus, there is a need for devices of laboratory analyzers, self-monitoring, closed-loop insulin delivery, and alarms connected with implantable sensors [207]. Advancement in biosensors entails the use of glucose sensors [175]. The extension of biosensor technology to tackle other important substrates is discussed, the principal hurdle to success being seen as the lack of long-term stability of the biological component [209].

Currently, the use of biosensors for the glucose analysis in physiological fluids or samples containing large glucose quantities (such as beverages, food products, and pharmaceutical preparations) was based on nanobiocomposite consisting of poly(1,10-phenanthroline-5,6-dione), poly(pyrrole-2-carboxylic acid), gold nanoparticles, and glucose oxidase was developed [210–213]. It is a reagent-less amperometric glucose biosensor, which has anti-interference capability to common interfering substances, good reproducibility, high long-term stability, and wide linear range [211,214,215]. In addition, it can be used to detect glucose in actual samples with good accuracy, which was confirmed by analyzing medical preparations [216,217]. Another application of biosensors is the *in vitro* model for evaluating glucose penetration through the skin [218]. The penetration spots nano holes in the skin as the main transdermal glucose penetration pathway [175,218].

4.2 TM

TM is an emerging technological advancement, which entails applying telecommunication systems to deliver health care remotely [219–221]. It can enhance patient health results, gain access to health care, and decrease health care expenses [222]. In 2015, Flodgren et al. assessed Cochrane Database Systematic Review, where they reported the efficiency and viability of applying TM to diabetic patients [219]. Their study concluded that TM involvement could give notable improvement and control blood glucose in comparison with typical diabetic care. The three main types of TM are real-time interactive services, *remote monitoring*, and store-and-forward. Each can provide substantial benefits for both healthcare personnel and patients [223,224].

Regardless of the factors of age and education level, there is a positive perception about TM among 75% of people with type 1 diabetes [225]. They considered TM beyond this COVID-19 pandemic. Nevertheless, poor glucose control generally in males appears to have a negative perception of TM [226].

In the case of T2D management, in addition to observing prescribed therapy and modified lifestyle, TM helps patients to adhere in various ways, such as reporting daily blood glucose assessments, a nurse could quickly respond to patient's health status and prescribe medication when needed, and facilitation of regular communication between patients and nurse case manager [227].

In line with GDM, researchers defined TM as health facilities and medical actions offered by healthcare professionals

via remote communication technologies [228–230]. Recently, information and communication technology introduced additional technological support for GDM clinical treatment [231]. The TM intervention is efficient in glycemic control and pregnancy outcomes in pregnant women with GDM because of its convenience in limiting face-to-face and impromptu consultations [231].

Gestational diabetes mellitus in women during the COVID-19 pandemic was remotely managed using a mobile phone application with artificial intelligence, which automatically classifies and analyses the data (ketonuria, diet transgressions, and blood glucose values), to make modification recommendations concerning the diet or insulin treatment [232,233].

5 Metallotherapy and diabetes treatment

The metals with antidiabetic and insulin-mimetic agents are chromium (Cr), cobalt (Co), manganese (Mn), molybdenum (Mo), selenium (Se), tungsten (W), vanadium (V), and zinc (Zn) [234]. They are useful as biomimetic drugs.

5.1 Choice for vanadium among other metals

Numerous applications of vanadium and its complexes seem to be the most potent among these metal complexes because the orally administered low concentration of vanadium complexes to animals prevented the onset of diabetes [234–236]. They also normalize BGLs of both type 1 diabetes and T2D [237–239]. Other factors contributing to the selection were based on availability, absorption, distribution, metabolism, transportation, and excretion [236].

5.1.1 Chemistry of vanadium metal

Vanadium has variable oxidation states ranging from -3 to $+5$ with the exception of -2 [240,241]. Among these oxidation states of vanadium, the commonest are $+2$, $+3$, $+4$, and $+5$. The oxidation states of vanadium, which are thermodynamically and physiologically stable and physiologically relevant are V^{3+} , V^{4+} , and V^{5+} [236,242,243]. Vanadium's oxidation states of $+3$, $+4$, and $+5$ bond readily with oxygen, nitrogen, and sulfur to form big complexes [244].

5.2 Biological activities of vanadium compounds

After 18 years of misconception that vanadium was carcinogenic and slightly toxic, it was ratified as an essential trace element with antidiabetic and anticarcinogenic properties [245–247].

Inkling for the use of vanadium compounds as insulin-mimetic agents among nutritionists arose when they discovered that vanadium was an essential element in some marine animals [248]. Vanadium is accumulated up to 0.7 g/kg in dry weight in macro fungi species such as *amanita muscaria* and peculiar species [249]. Further investigation was performed to support the synthesis of vanadium compounds, i.e., the two classes of natural vanadium enzymes, namely, vanadium nitrogenase and vanadase-dependent haloperoxidases [250,251]. Some nitrogen-fixing microorganisms such as *azotobacter* uses *vanadium nitrogenase*, where vanadium replaces molybdenum or iron, giving slight different properties to vanadium nitrogenase [252]. Another driving force to vanadium coordination chemistry was the medical uses observed when vanadate, peroxovanadate, vanadyl, and other vanadium complexes influence insulin-mimetic properties [253].

The deficiency of vanadium in animals and humans leads to retarded growth and reduced reproduction [254]. Vanadium possibly has glycemic control because of its insulin-mimetic properties in both *in vitro* and *in vivo* models of animals, thereby preventing the phosphotyrosine phosphatase (PTP) enzyme system [236,253].

5.2.1 Vanadium uses as antidiabetic and insulin-mimetic agents

According to Crans et al., vanadium's antidiabetic activities have been known for more than 100 years ago [243]. The activities entail vanadium compounds and its biological applications to diabetes. Vanadium compounds emerged as antidiabetic and insulin-mimetic agents for potential uses in diabetes therapy because they could mimic insulin in *in vitro* and *in vivo* systems against both type 1 diabetes and type 2 diabetes [236]. Antidiabetic treatment in animals with inorganic vanadium salts resulted in low absorption from gastrointestinal tracts, and side effects, such as gastrointestinal distress, reduced body weight gain, hepatic, and renal toxicities. Recently, studies showed that organic vanadium compounds were safer than inorganic vanadium salts

with little or no effects. Bis(maltolato)oxovanadium(IV) (BMOV) made excellent glucose-lowering impacts at an extraordinary lower dose without obvious sign of toxicity than early used inorganic vanadium salts [254]. They used maltol as the organic ligand to coordinate vanadium(IV) ion. Maltol (3-hydroxy-2-methyl-4-pyrone) is one of the numerous hydroxypyrones, long identified for high bioavailability and extremely approved toxicity profiles [255,256]. It is a recommended food additive applied to give a desired malty flavor and smell to beer, bread, cakes, and other beverages [257,258]. Its analogue ethyl-maltol (2-ethyl-3-hydroxy-4-pyrone) is also a recommended food additive [259]. Chemical structures of maltol and BMOV (ionic and neutral forms) are shown in Figure 9a and b, respectively. Adam et al. also reported that the insulin-mimetic antidiabetic efficacy of vanadium(IV) complex of vitamin A possesses enhanced antioxidant effect, kidney and liver functions, lipid profile, glutathione, malondialdehyde (MDA), and methionine synthase [260]. Conversely, Buglyó et al. were able to study the dipicolinate complexes in vanadium's three oxidation states (+3, +4, and +5) in a chronic animal model system [261]. Results from their studies revealed vanadium (v) dipicolinate complex as the most active to decrease the blood glucose level. They concluded that both ligand and metal oxidation states influenced the antidiabetic and insulin-mimetic activities of compounds [261].

Figure 9: (a) Chemical structure of maltol (ligand). (b) Chemical structure of bis(maltolato)oxovanadium(IV) (BMOV) in ionic (i) and neutral (ii) forms.

5.2.2 Metal nanoparticles as antidiabetic and insulin-mimetic agent

Lushchak et al. emphasized the enhanced antidiabetic and insulin-mimetic activities from metal nanoparticles with a dimension of 1–100 nm, very promising for T2D treatment because of their tuned physicochemical characteristics properties and capability to alter the oxidative stress level [262].

5.2.3 Vanadium nanoparticles as antidiabetic and insulin-mimetic agent

Vijay et al. concluded from their studies that vanadium nanoparticles are better antidiabetic and insulin-mimetic agents than vanadium complexes (organic vanadium) in controlling the biochemical parameters (reduced creatinine, serum glucose, triacylglycerol, total cholesterol urea, as well as, increased liver glycogen levels and serum protein) without any side effects [263,264]. In other words, results revealed improved glucose homeostasis.

6 Conclusion

The fourth type of diabetes and other types of diabetes that are recognized to be initiated by other factors like cystic fibrosis or by chemical induction were outside the scope of this study. As a result, this study dealt with type 1, type 2, and type 3 diabetes. This study gave an overview of the history of diabetes mellitus and how researchers around the globe contributed to control it from early years to this present moment. The content analysis was used as the methodological approach to assess researchers' impacts from the past to the contemporary era. An issue on animal models, which was held with ethical consideration, was highlighted to have helped to boost diabetic studies. Nanotechnology brought illumination to diabetes treatment. The safety of nanomedicine is to be ensured for biocompatibility and desired results. Recent studies and developments entail the diagnosis and treatment of diabetes mellitus with the eminent roles and applications of biosensors and TM. Biosensors are applied in glucose analysis and glucose penetration in the skin, while TM helps to deliver health care remotely to diabetic people. In metallotherapeutic approach to diabetes treatment, vanadium and its coordination compounds were selected because they were the most potent among other metal coordination compounds, can be

orally administered at low concentration to animals, and other numerous factors based on availability, absorption, distribution, metabolism, transportation, and excretion. Vanadium nanoparticles (metal nanoparticles) also provided enhanced glucose homeostasis. The application of vanadium nanoparticles will help to solve the drawback experienced because of antidiabetic drugs sold to diabetic patients and limit the use of injection during the administration of insulin.

7 Future research

Future research will entail the comparative studies of oxovanadium(IV) nanoparticles and zinc(II) nanoparticles as antidiabetic and insulin-mimetic agents.

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