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Progress in Diabetes Mellitus Treatment

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Abstract. Hyperglycemia, a chronic condition caused by either absolute or relative insufficiency of insulin production and poor insulin utilisation, is the hallmark of diabetes mellitus. Type 1, type 2, and gestational diabetes are the three primary classifications of the condition. The primary cause of the illness is thought to be a confluence of environmental and genetic factors, such as the body's insensitivity to the effects of insulin or a decrease in insulin secretion brought on by pancreatic islet cell dysfunction, which both impede the body's ability to use and store blood glucose. Diabetes has a long history of development. The disease was first named diabetes in the Yellow Emperor's Neijing patients who had polyphagia, polydipsia, polyuria, and weight loss. Of course, the disease's treatment history is even longer, beginning with the discovery of insulin and continuing with a gradual analysis of the pathology of diabetes and other therapeutic techniques to improve diabetes treatment. Currently, insulin injections, which work on the principle of promoting glucose, are used to treat diabetes. Insulin is currently administered intravenously to treat diabetes. Insulin helps control blood glucose levels by enhancing glucose absorption and utilisation, preventing the release of hepatic glycogen, and encouraging the synthesis of fatty and amino acids. This article contains the history of the development of the disease, the first panel is the background, in the history of the development of the disease is divided into the history of the discovery of diabetes and the history of the treatment of diabetes, in the discovery of diabetes in the history of the panel only lists the important historical nodes, in the history of medical treatment of diabetes is written from the beginning of the discovery of insulin once in 1921, a lot of scientists have made their own unique contribution to diabetes. The clinical features of the disease are of course included, as well as an overview of the most common insulin treatments available. The second panel is an introduction to the pathogenesis of diabetes mellitus, which addresses the relevant mechanisms of diabetes mellitus and includes important proteins of interest in the pathogenesis of diabetes mellitus. The third panel is an overview of the treatment modalities, the four current treatment modalities, and my thoughts on how to improve them.

Keywords: Diabete, therapy, insulin, protein.

1. Introduction

An excessive drinking and urinating sickness were documented in a text left by ancient Egyptians in 1550 B.C. This is the first literary account of diabetes that can be traced back to archaeology. A condition with symptoms resembling modern-day diabetes, such as excessive eating, drinking, urinating, and weight loss, was described about 400 B.C. in the Chinese Yellow Emperor's Classic of Internal Medicine.

The disease was renamed as diabetes mellitus in 1675 thanks to a paper published by Englishman Thomas Willis and renowned English physician John at the time.

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English physician Matthew Dobson made the further discovery in 1776 that diabetics' blood serum had an equal amount of sugar to urine. This finding suggested that diabetes was a long-term, systemic illness [1].

In 1921, By refining a pancreatic extract, Frederick Banting and Charles Best discovered insulin. Later, they were able to isolate insulin from canine subjects, induce diabetic symptoms in the animals, and begin insulin injections to restore normalcy to the canines. Leonard Thompson, 14, also made history by being the first person with type 1 diabetes to get insulin injections. After about a year, Banting and McLeod were granted the Nobel Prize for their discovery of insulin, which was refined to effectively treat diabetes [2]. In 1955, Dinitrofluorobenzene was used in a technique developed by Sanger to create derivatives of yellow amino acids (see amino acid). Recent publications have provided details on distribution chromatography, a novel method of separation. He saw right away the value of this novel method for distinguishing the hydrolysis products of treated proteins, as is characteristic of a Sanger career. He discovered that phenylalanine and glycine are the two terminal amino groups of insulin, indicating that the protein is made up of two different kinds of chains. Sanger studied the amino-terminal regions of several other proteins using this technique, as did Rodney Porter, his first graduate student [3]. In 1958 Frederick Sanger won the Nobel Prize in Chemistry. Important histological discoveries were published that revealed the pathological anatomy of diabetes after ten years. The classical view was that T1D was caused by a severe deficiency of insulin-producing tissues, resulting in an absolute deficiency of insulin secretion, and Glycosylated hemoglobin appear in 1971, which test is used to assess a person's level of blood sugar control. It can diagnose diabetes [4].

Yalow and Berson's theory, which won the 1977 Rosalyn Yalow Nobel Prize in Physiology or Medicine, was that foreign insulin induced the formation of antibodies, which bind to the hormone and prevent it from entering the cell and doing its job of metabolizing glucose. When the scientists measured the traces of these antibodies using a combination of immunological and radioisotope monitoring methods, RIA was created. It was quickly found that hundreds of other physiologically active molecules, including viruses, medications, and other proteins, could be measured using this technique. The study of drugs advanced greatly as a result of this. It also demonstrated that insulin deficiency was not the cause of type 2 diabetes; rather, it was the body's incapacity to use insulin efficiently.[5]

The discovery of the first autoantigen in 1982 marked a significant advancement. Baekkeskov and associates discovered autoantibodies to this islet protein by immunoprecipitation tests, which were absent from normal serum. Numerous autoantibody targets have been found, and research on autoantigens is still ongoing. Along with helping research into disease prevention and the development of antibody tests that are still in use today, such as GAD65, insulinoma-associated protein 2, zinc transporter 8, and insulin autoantibodies, which are frequently used to predict and confirm the diagnosis of T1D, this also provided evidence that type 1 diabetes is an autoimmune disease [6].

GLP-1 was discovered in 1987 by Habener and Holst's labs to be a crucial regulator of the ileocecal brake, an enteric insulinotropic hormone that also serves as a brake. Following the discovery that GLP-1 is a physiological inhibitor of food intake, GLP-1 agonists are regarded as one of the most powerful and successful antiobesity and antidiabetic medications available today. They also have the added advantage of lowering the risk of cardiovascular and renal complications linked to these diseases. illnesses with the bonus of lowering the chance of cardiovascular and kidney problems brought on by these illnesses. illnesses that also have the added benefit of lowering the chance of problems related to the heart and kidneys. This has aided in the development of enteroglucagon-based treatments for type 2 diabetes. A monoclonal antibody that selectively targets glucose transporter proteins was created by James et al. a year later. Insulin facilitates the absorption of glucose by adipocytes and cardiomyocytes and is necessary for maintaining glucose homeostasis. One antibody was found to be highly selective for a protein that was subsequently molecularly cloned and identified as the insulin-regulated glucose transporter protein. The experiments were conducted by immunizing mice with purified intracellular membranes believed to be enriched in insulin-responsive glucose transporter proteins. Molecular cloning was used to identify the protein as an insulin-regulated glucose transporter protein, which was subsequently given the name GLUT4. This work demonstrated that the production of GLUT4, a distinct

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glucose transporter protein, is required for insulin-stimulated glucose absorption in these tissues and that insulin signaling controls GLUT4 intracellular transport [7].

Pories et al. reported a remarkable remission of type 2 diabetes mellitus in a sample of obese patients who received bariatric surgery in 1995, the year when the procedure became relevant in the field of diabetes. Adults with type 2 diabetes have improved or gotten rid of their condition thanks to bariatric surgery. It has also been recommended by some clinical researchers as an early treatment strategy for type 2 diabetic patients who do not fit the requirements for bariatric surgery. The precise processes underlying the metabolic implications remain largely unknown, and research on the hormonal modifications leading to the remission of diabetes is currently ongoing. Bariatric surgery is still one of the best ways to address this condition nowadays. Five years later, researchers examined the connection in 333 Scandinavian parent-child pairs to learn more about the genetics of T2D. Three further research groups with European heritage had their replication of the alleles exhibiting nominal relationships evaluated. PPARG is a type 2 diabetes susceptibility gene, as demonstrated by this investigation. Over 550 risk signs for type 2 diabetes have been found to far, indicating significant advancements in this sector. These genetic variables have provided invaluable information that has been applied to research on disease processes and treatments, and it may serve as a springboard for future advances in precision medicine [8].

In 2006, stem cell therapy emerged as a major advance in the treatment of diabetes. Because of its immunomodulatory qualities and capacity to replenish insulin-producing cells, stem cells have demonstrated substantial therapeutic potential in diabetic patients. Haematopoietic stem cells (hsc) were employed by Volarelli et al. to treat newly diagnosed T1DM patients by transferring insulin-producing the ultimate therapy, or perhaps a cure, for type 1 diabetes may involve transplanting insulin-producing pancreatic β-cells to replace the declining quantities of insulin in affected people. This groundbreaking work described for the first time the in vitro differentiation of human embryonic stem cells into hormone-secreting endocrine pancreatic cells. These cells were able to produce and release insulin, exhibit beta cell markers, and show very little glucose sensitivity. Additionally, once a year had passed, islet inflammation in type 2 diabetes became apparent. Mark Donath and colleagues discovered that islet-derived inflammatory factors, which are induced by the excess circulating nutrients in the T2D environment, result in macrophage infiltration of islets. This finding implies that insulin plays a role in both type 2 and type 1 diabetes, and that pancreatic islet inflammation is a pathognomonic feature of both conditions. These findings open up new avenues for investigating the role of inflammasome activation and anti-inflammatory therapy [9].

In 2012, the initial clinical trials involving Treg cells demonstrated that apoptotic Treg cells had more immunosuppressive potency compared to live Treg cells. Additionally, they were more successful in suppressing T cell production of TNF, IL-2, and IFN-γ. Furthermore, in colon cancer-stricken animals, apoptotic Treg cells inhibited both spontaneous and PD-L1 inhibitor-mediated anti-tumour T cell immunity, which encouraged the development of tumors. These studies proved the safety and tolerability of this strategy, as well as its favorable initial effectiveness [10].

The most recent advancement is the successful 2016 islet transplant at Changzheng Hospital, which was Shanghai's first such procedure. The 67-year-old patient had diabetes-related renal failure, but the doctor advised islet transplantation because: kidney transplantation cannot address the underlying cause of diabetes; the transplanted kidney will continue to be affected by blood sugar fluctuations, and it is typically necessary to undergo kidney transplantation again approximately seven years following the procedure; and international data indicates that islet transplantation can effectively control blood sugar and extend the life of the transplanted kidney by 2.5 times. Additionally, a Phase III experiment has shown that transplanting pure human islets improves glycemic control, raises awareness of hypoglycemia, and reduces severe hypoglycemic episodes in individuals with Type 1 diabetes [11].

2. Mechanism

An essential source of energy for the cells that make up muscles and tissues is glucose. Type 1 and type 2 diabetes are both considered forms of chronic diabetes. Increased water intake, larger meals, increased

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urination, progressive weight loss, skin infections, exhaustion, and visual abnormalities are typical signs of type 1 diabetes. The onset of type 2 diabetes often happens after the age of 40, and in its early stages, half of the patients have no symptoms. Obesity, dyslipidemia, and high blood pressure are other common companions of type 2 diabetes. Gestational diabetes and prediabetes are examples of diabetes that may be reversible. When blood sugar levels are greater than usual, precursor diabetes develops. Blood sugar levels are not high enough, though, to qualify as diabetes. If preventative steps are not performed, diabetes may result from precursor diabetes. Diabetes during gestation happens during pregnancy. However, it can vanish once the baby is delivered. Insulin injections are now the most widely used treatment for diabetes. They function by increasing the absorption and utilisation of glucose, preventing the release of hepatic glycogen, and encouraging the synthesis of fatty and amino acids. First and foremost, insulin encourages cells to absorb and use glucose. Insulin acts by binding to the insulin receptor on the cell surface. This complex then forms and facilitates the transport of the glucose transporter protein to the cell membrane, opening the GLUT4 channel and allowing glucose to enter the cell and be rapidly metabolized within. In addition, insulin has the ability to prevent the liver's stored glycogen from being broken down and from releasing glucose through the process of glycogenolysis, thereby preserving the body's supply of energy. Lastly, insulin also encourages protein synthesis, the fatty acid and amino acid conversion into fatty esters, and storage in fat, the liver, and other tissues. To put it briefly, insulin can aid in controlling blood sugar levels and the advancement of diabetes. For this reason, one of the primary strategies for controlling blood sugar in diabetics is insulin replacement treatment [12].

2.1. T1D

About 5–10% of all instances of diabetes are caused by T1D. It's an autoimmune illness where pancreatic β-cells are destroyed by T cells, which causes insulin insufficiency and hyperglycemia in the end. Although the pathophysiology of this autoimmunity is still unclear, genetic and environmental variables have been discovered to have an impact. The eventual course of the illness is often determined by variations in the pace of immune-mediated death of pancreatic β-cells. Autoantibodies, in particular, are among the immunological markers that define type 1 diabetes. The disease-causing immune-mediated death of β-cells is linked to these autoantibodies. Autoantibodies encompass a variety of substances, such as insulin autoantibodies (IAAs), pancreatic islet cell β-cytoplasmic protein autoantibodies, tyrosine phosphatase IA-2 and IA-2α autoantibodies, zinc transporter protein isoform 8 (ZnT8) autoantibodies, and glutamic acid decarboxylase autoantibodies (GADAs) like GAD65. The most significant of these autoantibodies is GAD65, which is seen in around 80% of T1DM patients at the time of diagnosis. 69–90% of ICAs and 54–75% of T1DM patients with IA-2α at the time of clinical presentation are the next most common types. Type 1 diabetics require lifelong insulin therapy since the pathophysiology of the disease is predominantly an autoimmune issue, which is demonstrated by the development of a complete absence of insulin in the patient as a result of autoimmunity. One subtype of glutamic acid decarboxylase antibody is GAD65 antibody, also known as glutamic acid decarboxylase 65 antibody. Type 1 diabetes is an organ-specific, insulin-dependent autoimmune disease. Patients with type 1 diabetes have high levels of autoantibodies in their blood, including antibodies to insulin, pancreatic islet cells, and glutamic acid decarboxylase. These three types of antibodies are present during the clinical examination of diabetes. The three antibodies mentioned above serve as both diagnostic criteria for diabetes type and an important part of the clinical assessment process. The criterion used to differentiate type 1 diabetic patients from type 2 diabetic patients and normal people is the presence of glutamic acid decarboxylase antibody, which is the first antibody to appear in the blood of type 1 diabetic patients. This antibody is absent from the blood of type 2 diabetic patients and normal people.

2.2. T2D

Roughly 90–95 percent of instances of diabetes are caused by T2D. This kind of diabetes is mostly brought on by insulin resistance and malfunctioning beta cells. A reduction in the sensitivity or reactivity of peripheral tissue cells to insulin is the cause of insulin resistance, which is brought on by the disruption

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of several cellular pathways. Throughout the course of the condition, pancreatic β-cell activity gradually declines, which is part of the pathophysiology of type 2 diabetes. The key to reversing diabetes is restoring the patient's β-cell activity and insulin sensitivity, which may be demonstrated by their ability to maintain excellent glycaemic control over an extended length of time even when the intensity of their glucose-lowering medication is reduced. When the illness is still in its early stages, the body's normal glycaemic balance is maintained by reducing insulin levels because lower insulin sensitivity causes β-cell hyperfunction, which results in an increase in insulin production as a compensatory measure. In order to preserve the body's typical glycaemic balance, β-cells release insulin to make up for the insulin that was previously secreted. Following this, the function of β-cells begins to decrease, and ultimately, β-cell malfunction results in insulin insufficiency. As a result, blood sugar equilibrium cannot be maintained when insulin levels fall. The majority of the time, insulin production is adequate to stop DKA from happening. On the other hand, highly stressful situations can cause DKA, and some drugs like corticosteroids or sodium-glucose cotransporter-2 inhibitors might make it worse. This kind of diabetes is caused by a complex interaction between powerful environmental factors and genetics [13]. In contrast to type 1 diabetes, the illness is not linked to genes that are involved in the immunological response, meaning that pancreatic β-cells are not destroyed by the immune system. Additionally, the pathophysiology and macrovascular consequences of type 2 diabetes are significantly influenced by chronic inflammatory variables. The entire process of atherosclerosis is caused by stimulating the production of tissue factor in the vasculature, activating the intravascular complement system, and other processes. A chronic inflammatory response may be one of the major causes of B-cell apoptosis in type 2 diabetes mellitus. This leads to a marked increase in the risk of macrovascular lesions and cardiovascular events in patients with diabetes mellitus [14].

2.3. GDM

GDM is a condition of reduced glucose tolerance or diabetes that occurs in women during pregnancy. It usually occurs in the middle of a woman's pregnancy, and most people with GDM return to normal blood sugar and glucose tolerance at the end of pregnancy. However, if the condition is severe, it can have serious consequences for the development of the foetus and for the pregnant woman herself. Risk factors for GD M include, firstly, obesity, which is an important risk factor. Secondly, there is a family history of diabetes. If a pregnant woman's parents have diabetes, the risk of GDM is nearly three times higher than that of an average pregnant woman. In early pregnancy, fasting and postprandial blood glucose levels are usually lower than normal, but in the third trimester, blood glucose levels rise to diabetic levels, a condition known as GDM. Pregnant women with GDM are more likely to have miscarriages, preterm births, stillbirths, and have a significantly lowered resistance to other complications, such as urinary tract infections. A glucose tolerance test can be performed to detect GDM, and the treatment for GDM is insulin rather than oral hypoglycaemic drugs, which pass through the placenta into the foetus and cause hypoglycaemia, resulting in a risky foetal birth [15].

3. Therapeutic method

3.1. Using insulin analogues

The new proteins are obtained by substituting or transposing individual amino acids. In the case of Pramlintide, a drug that has now been studied, Pramlintide gains resistance to fibre formation by replacing alanine, serine and serine at positions 25, 28 and 29 with proline. The proline residue gives the peptide chain rigidity due to its unique cyclic structure. This rigidity disrupts -sheet formation, a common structural feature of amyloidogenic fibrils. By preventing the formation of beta -sheets, proline peptides remain in a more soluble and non-aggregated form, enhancing their therapeutic properties. So, proline introduces a kink in the peptide chain that disrupts the ability of the molecule to adopt the extended conformation necessary for amyloid fibril formation. This modification stabilises the proline peptide and makes it suitable for therapeutic use as it reduces the risk of amyloid-related toxicity and ensures that the peptide remains soluble and functional when administered to diabetic patients.

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3.2. Activation of glucagon-like peptide-1 receptor

It can lower glucose, reduce body weight, and can protect cardiovascular and cerebral vessels. Glucagon-like peptide-1 receptor agonists, or GLP-1 receptor agonists, are a class of drugs used to treat type 2 diabetes. This class of drugs can produce glucose-lowering effects by agonising the glucagon-like peptide-1 receptor and exerting the effects of enteric proinsulin, and is a class of proinsulin secretion drugs that can lower both blood glucose and body weight, and also show advantages in cardiovascular protection.GLP-1 agonists are able to glucose-dependently promote the secretion of insulin.GLP-1 agonists promote the release of insulin mainly by activation of the GLP-1 receptor. In addition to promoting insulin synthesis and secretion, GLP-1 also inhibits glucagon secretion, stimulates β-cell proliferation and neogenesis, inhibits β-cell apoptosis, reduces feeding, delays gastric emptying, and has potential protective effects on cardiomyocytes.

3.3. Regulating the immune system through immunomodulatory proteins

Type 1 diabetes is a disease triggered by the immune system's attack on pancreatic beta cells, and immunomodulatory proteins are designed to slow or prevent this attack by regulating the immune system's response. Immunomodulatory proteins can slow or prevent the attack on pancreatic beta cells by regulating the activity of the immune system. The autoimmune response is then inhibited: damage to pancreatic beta cells is reduced by inhibiting immune cells that produce antibodies specific to pancreatic beta cells. The therapeutic effect with immunomodulatory proteins can firstly help to restore the tolerance of the immune system to its own tissues and reduce the attack on pancreatic islet cells. Secondly it can protect pancreatic beta cells because certain immunomodulatory proteins may have a protective effect on pancreatic beta cells, reducing their apoptosis or loss of function. Finally, it can regulate immune cell function Immunomodulatory proteins can alter the function of immune cells, for example by regulating T-cell activity. The potential of immunomodulatory proteins in diabetes treatment focuses on the protection of pancreatic β-cells and the reduction of autoimmune responses by modulating the immune system.

3.4. C-peptide

C-peptide is an important molecule in the synthesis of insulin, which is secreted by pancreatic β-cells together with insulin and remains in the blood after the release of insulin. His role has pancreatic beta cell function protection. Research suggests that C-peptide may protect pancreatic beta cells by reducing oxidative stress and inflammation, which in turn slows the progression of diabetes. The second is that C-peptide may help improve vascular function in diabetics. Several studies have found that C peptide may improve endothelial cell function and reduce endothelial damage in blood vessels, which is beneficial to cardiovascular health in diabetics. Finally, C peptide may help control blood sugar levels by promoting glucose uptake and utilisation and improving insulin sensitivity. In type 1 diabetes the role of C-peptide in type 1 diabetes has received a lot of attention. Since type 1 diabetes results from an autoimmune attack on pancreatic β-cells, the protective effects of C peptide may help slow the progression of the disease and improve pancreatic β-cell function in patients. In type 2 diabetes, the role of C-peptide may be primarily in improving insulin resistance and protecting vascular function. Although C-peptide does not directly affect pancreatic β-cell secretion, its potential to improve metabolic and vascular function makes it an interesting area for research.C-peptide is commonly used to assess pancreatic β-cell function. By measuring C-peptide levels in the blood, doctors can learn about the remaining function of pancreatic beta cells and the progression of diabetes.

4. Conclusion

Based on the several treatments currently available, I have some improvements to make first with insulin analogues in addition to amino acid substitutions, I think there are other ways to obtain insulin analogues as well, such as structural modifications, which modify the structure of the insulin molecule, for example, by adding or removing certain chemical groups to the chain end of the insulin. Such modifications can alter the stability of insulin or the way it is metabolised in the body. Finally, insulin is combined with

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other molecules by binding carriers to alter its release characteristics. These modifications are intended to improve the pharmacodynamic properties of insulin, such as shortening the onset of action, lengthening the duration of action, or reducing side effects. Each type of insulin has its own specific scenarios of use and advantages and disadvantages, and the appropriate insulin preparation is selected based on the patient's specific situation. The second method of activating the glucagon-like peptide-1 receptor, an agonist, with a bad side effect can lead to nausea and headache, and I believe that it is entirely possible to reduce the adverse effects by means such as purification, such as high-performance liquid chromatography (HPLC) or affinity chromatography, which removes impurities or by-products that may be present in the drug. These impurities can lead to additional adverse reactions, so improving the purity of the drug can reduce these reactions or with optimised formulation processes, where the purification and formulation processes are optimised to ensure the stability and release characteristics of the drug in the body during the drug formulation process. This can help to reduce the side effects and improve the tolerability of the drug. The third approach is still in the research stage, and the potential of immunomodulatory proteins in diabetes treatment is mainly in the protection of pancreatic β-cells and the reduction of autoimmune reactions by modulating the immune system. The last technique regarding C-peptide is currently more mature and there is no better way to improve it.

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