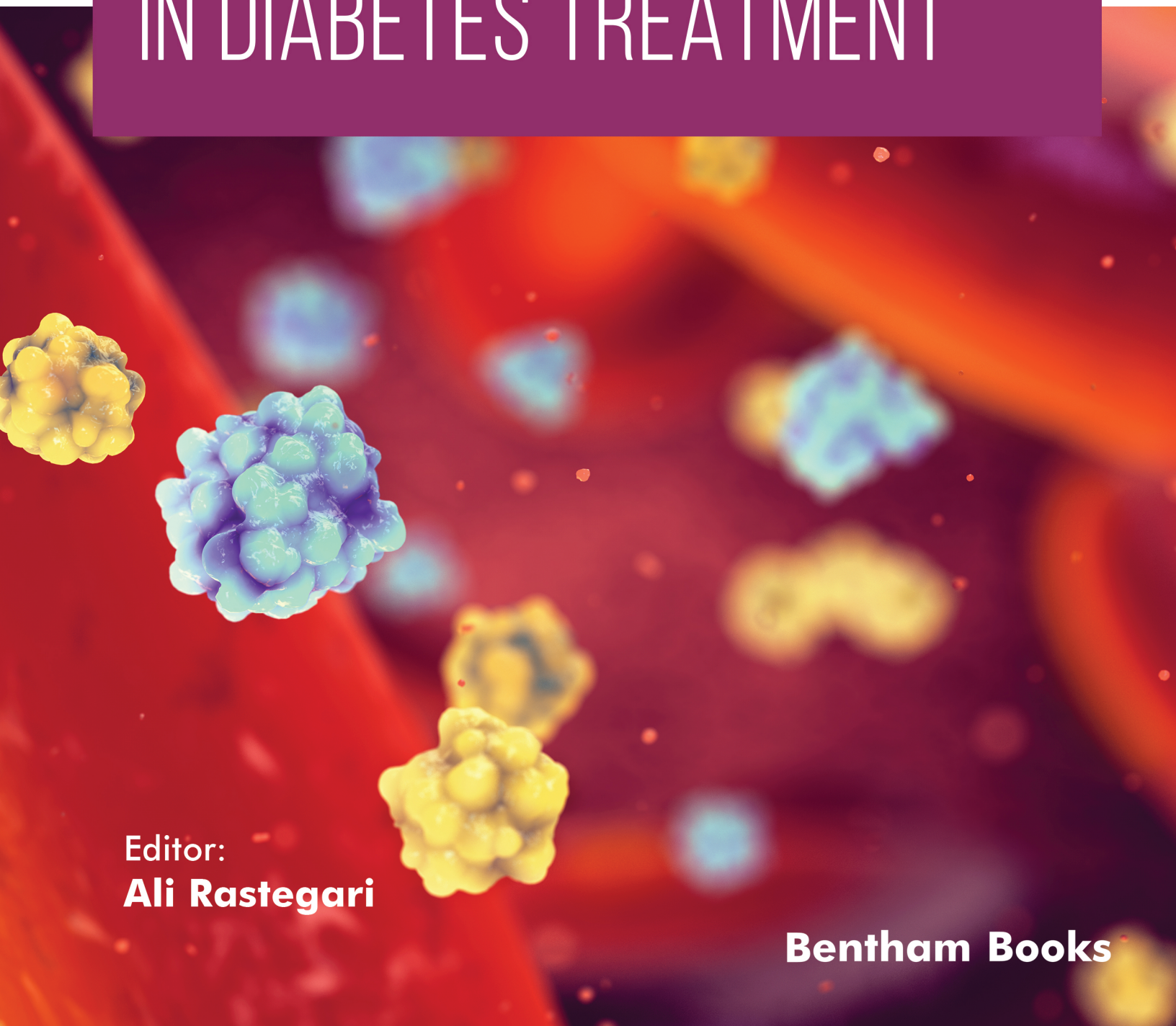
NANOSCIENCE APPLICATIONS IN DIABETES TREATMENT



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PREFACE

The book is structured in a manner that sequentially covers various aspects related to diabetes and the application of nanotechnology in its treatment. Chapters 1 and 2 extensively delve into the pathophysiology of diabetes, encompassing different types of the disease, and provide an overview of the diverse medical therapy approaches available for each type. Chapter 3 focuses on the utilization of nanomedicine for insulin delivery in diabetes treatment. It thoroughly explores the various nano-based vehicles that hold the potential for delivering insulin effectively. In Chapter 4, the book extensively discusses the potential of nanoscience in drug delivery for diabetes. This chapter presents a comprehensive review of different studies that have investigated the use of nanoparticles as carriers for drug delivery in diabetes treatment. The final chapter concentrates on nanotechnology approaches for nucleotide delivery and gene therapy in diabetes. It not only highlights the advancements in this field but also addresses the associated challenges and potential future developments. Overall, the book aims to provide a comprehensive understanding of diabetes, current medical therapies, and how nanotechnology can be harnessed to enhance treatment options, including insulin delivery, drug delivery, and gene therapy.

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List of Abbreviations

AGIs Alpha-glucosidase inhibitors
BMI Body mass index
CDC Centers for disease control and prevention
CPPs Cell-penetrating peptides
CNTs Carbon nanotubes
DM Diabetes mellitus
DDs Drug delivery systems
DPPi Dipetidyl peptide inhibitor
DNA Deoxyribonucleic acid
FDA Food and drug administration
G-CSF Granulocyte colony-stimulating factor
GAD Glutamic acid decarboxylase
GI Gastrointestinal
GLP-1 Glucagon-like peptide-1
GIP Gastric inhibitory polypeptide
GCK Glucokinase
GLB Glibenclamide
HLA Human leukocyte antigen
IL Interleukin
ICAs Islet cell antibodies
IAAs Insulin autoantibodies
LPL Lipoprotein lipase
LADA Latent autoimmune diabetes of adults
LNCs Lipid nano-capsules
MNPs Metallic nanoparticles
MODY Maturity-onset Diabetes of the Young
MCP1 Monocyte chemoattractant protein 1
MEs Micro-emulsions
NPs Nanoparticles
NEs Nano-emulsions
NLCs Nanostructured Lipid Carriers
PKC Protein kinase C

PLs Pro-liposomes

PEG Poly ethylene glycol

PLGA Poly (lactic-co-glycolic) acid

RAA Rapid-acting analogs

RNA Ribonucleic acid

SiRNA Short interfering RNAs

SGDC Sodium-glycodeoxycholate

SLNs Solid lipid NPs

SUR Sulfonylurea receptor

SGLT2 Sodium-glucose cotransporter 2

TCA Tricarboxylic acid

TZD Thiazolidinediones

TNF Tumor necrosis factor

T1DM Type 1 diabetes mellitus

T2DM Type 2 diabetes mellitus

UCP1 Uncoupling protein 1

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CHAPTER 1

The Story of Diabetes and its Causes

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Abstract: Diabetes mellitus (DM) is a complex metabolic disorder whose rising prevalence is terrible. A deeper knowledge of the pathophysiology of diabetes could assist in discovering possible therapeutic targets for treating diabetes and its associated problems. The common feature of diabetes, regardless of the specific pathology involved, is hyperglycemia brought on by the death or dysfunction of β-cell. As insulin deficiency gets worse over time, dysglycemia progresses in a continuum. This chapter has provided a brief review of the pathophysiology of diabetes. Also, the roles of genetics and environmental factors have been emphasized.

Keywords: Diabetes, Disease, Factor, Glucose, Pathophysiology.

INTRODUCTION

Diabetes mellitus is a complex metabolic disorder whose principal clinical and diagnostic feature is hyperglycemia [1]. Diabetes has reached epidemic proportions; the global diabetes prevalence in 20-79-year-old in the latest reports was estimated to be 10.5% (536.6 million people), rising to 12.2% (783.2 million) in 2045 [2]. Over the next 20 years, its prevalence is expected to double, affecting more than half a billion people, with more than 75% of patients living in low- and middle-income countries [3]. Additionally, the increase in prevalence in developing countries is believed to be greater due to the widespread adoption of Western lifestyle habits, such as sedentary behavior, inactivity, and a high-energy diet [4, 5].

The risk of a variety of cardiovascular disorders is roughly doubled by diabetes, particularly type 2 diabetes mellitus (T2DM) [6]. In addition, a wide range of non-vascular diseases, such as cancer, infections, liver disease, and mental and nervous system disorders, are linked to T2DM [7]. In a similar vein, type 1 diabetes mellitus (T1DM) is linked to an increased risk of both vascular and non-

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vascular complications. A deeper knowledge of the pathophysiology of diabetes could assist in discovering possible therapeutic targets for treating diabetes and its associated problems [8, 9].

TYPE 1 DIABETES

The prevalence of T1DM is increasing worldwide. Although T1DM is often diagnosed in childhood, 84% of people living with T1DM are adults [10]; 62% of all new T1D cases in 2022 were in people aged 20 years or older [11]. T1DM affects men and women equally [12] and reduces life expectancy by an estimated 13 years [9]. With some exceptions, the incidence of T1DM is positively related to geographic distance north of the equator [13]. Colder seasons correlate with the diagnosis and progression of T1DM. Both disease onset and the incidence of islet autoimmunity appear to be higher in autumn and winter than in spring and summer [14 - 16].

Role of Genetics

The higher prevalence of T1DM in a family suggests a hereditary risk, which increases with the proband's degree of genetic similarity. Human leukocyte antigen (HLA) gene variations alter how the HLA protein binds to antigenic peptides and how the antigen is presented to T cells, contributing to 50-60% of the gene risk. Cell surface proteins involved in antigen presentation and self-tolerance are encoded by HLA genes, which are essential for controlling the immune response. As a result, genetic variations in these proteins' amino acid sequences may alter the repertoire of presented peptides and result in self-tolerance loss [17].

The autoimmune nature of diabetes is primarily due to its strong connection to HLA, the DQA and DQB genes, and its direct influence through the DRB genes [18]. Genome-wide association studies have demonstrated a strong link with the HLA-DR3 and HLA-DR4 haplotypes, as well as an exclusive link between the autoimmune destruction of β-cells and the DR4-DQB1I0302 haplotype [19 - 21].

Smaller effects are caused by about additional 50 genes individually [22, 23], including gene variants that modulate immune regulation and tolerance, viral responses [24 - 29], responses to environmental signals, and endocrine function [30]. Some variants are expressed in pancreatic β-cell [31]. In relatives, the onset and progression of islet autoimmunity are influenced by genetics [32, 33]. These gene variants collectively are responsible for 80% of T1DM inheritance [34]. A patient's risk, C-peptide decline rates, and response to various therapies can all be predicted by genetic variants [35]. With a deeper comprehension of heredity profiles, new goals for individualized interventions may be realized.

Role of the Environment

Numerous pieces of evidence suggest that environmental and genetic factors interact to cause autoimmunity and the development of T1DM, such as T1DM discordance rates in twins, the variance in geographic prevalence, and the adjustment of disease incidence rates as individuals migrate from low to high-incidence countries. The fact that most patients with the highest risk HLA haplotypes do not develop T1DM lends credence to this gene-environment interaction. Timing of environmental trigger exposure can also be very important. The investigation of environmental exposures is made more challenging by the variation in disease onset age. However, the early onset of islet autoantibodies linked to T1DM in children raises the possibility that early environmental exposures may play a role [10].

Infection

Congenital rubella infection has strong evidence to raise the possibility of T1DM development [36]. Enteroviruses are also thought to be associated with T1DM [37]. These infections are considered to alter gut microbiome composition [10].

Dietary Factors

β-cell autoimmunity can be affected by the timing of exposure to foods like grains and nutrients like gluten [10], as some studies show that early initiation of (<3 months) cereals may have this effect [38]. Retrospective studies led to the hypothesis that early initiation of cow's milk or less breastfeeding could increase the risk of T1DM. However, it was not confirmed by prospective studies [39]. Vitamin D deficiency and low levels of omega-3 fatty acids have been probably linked to an increased risk of T1DM [40].

Natural History and Prognosis

The common feature of diabetes, regardless of the specific pathology involved, is hyperglycemia brought on by the death or dysfunction of β-cell. As insulin deficiency gets worse over time, dysglycemia progresses in a continuum. The ability to categorize diseases and determine where and how to intervene best to stop or halt disease progression and complications depends on understanding the natural history of β-cell mass and function [10]. T1DM pathogenesis is influenced by both humoral and cellular immunity [41]. There is increasing evidence of significant overlap across the entire spectrum of diabetes, even though T1DM is caused by the immune system's destruction of beta cells, and T2DM is mostly associated with glucose-specific insulin secretion problems [42]. In both types of diabetes, the hyperglycemia-induced stress response may contribute to β-cell

CHAPTER 2

Treatment Approaches and Challenges

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Abstract: Diabetes drugs are given in monotherapy or in combination. The significant challenges in effective diabetes management are optimizing current treatments to ensure optimal and stable glucose control with minimal side effects and reducing long-term complications of diabetes. This chapter reviews these conventional drugs with their mechanism of action, side effects, and efficacy and safety profile.

Keywords: Diabetes, Disease, Safety, Treatment.

INTRODUCTION

Many people worldwide are affected by diabetes mellitus (DM), a significant public health problem [1]. The worldwide increase in diabetes patients, maybe primarily attributable to the trend toward sedentary living [2]. Retinopathy, nephropathy, neuropathy, and cardiovascular complications are DM-related complications [3].

Diabetes drugs are given in monotherapy or combination [4]. The significant challenges in effective diabetes management are optimizing current treatments to ensure optimal and stable glucose control with minimal side effects and reducing long-term complications of diabetes [5]. Nanoformulations can solve some of the disadvantages of current anti-diabetic drugs [5] and, more importantly, promote cellular uptake and enhance the pharmacokinetics and pharmacodynamics of drugs [6].

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PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 1 DIABETES

Insulin Therapy

Insulin treatment is essential for these individuals because the absence or near-absence of β-cell function is the hallmark of T1DM [7]. Furthermore, during the past three decades, there has been growing evidence that the optimal combination of effectiveness and safety for patients with T1DM is provided by more intense insulin replacement, such as numerous daily insulin injections or continuous subcutaneous delivery *via* an insulin pump [8 - 10].

Basal insulin, prandial insulin, and correction insulin are frequently used in insulin replacement therapy [11]. NPH insulin, long-acting insulin analogs, and continuous rapid-acting insulin delivery *via* an insulin pump are all components of basal insulin. Compared to NPH insulin, basal insulin analogs have a longer duration of action and plasma concentration and activity profiles that are flatter and more constant. Compared to standard human insulin, rapid-acting analogs (RAA) have a quicker onset, peak, and duration of action. Compared to human insulin, treatment with insulin analogs is associated with lower HbA1C and less hypoglycemia, weight gain, and hypoglycemia in T1DM patients [12 - 14]. Compared to RAA, inhaled human insulin may cause less hypoglycemia and weight gain due to its rapid peak and shorter action duration [15]. Recently, two new formulations of injectable insulin were released with improved fast-acting profiles. Faster-acting insulin aspart and insulin lispro-aabc are better at reducing prandial excursions than RAA [16, 17]. In addition, compared to U-100 glargine, longer-acting basal analogs (U-300 glargine or degludec) may reduce the risk of hypoglycemia in T1DM patients [18, 19]. Despite the advantages of insulin analogs for T1DM patients, some people cannot afford the expense and level of care needed to utilize them [20].

There are numerous insulin treatment options. In order to prevent diabetic ketoacidosis, avoid severe hypoglycemia, and meet individual glycemic goals, the administration of some form of insulin in a planned, individualized regimen is essential for T1DM treatment [20]. By altering the original insulin molecule and changing its constituent parts, several other forms of insulin molecules have developed [20]. These insulin analogs' pharmacodynamic and pharmacokinetic profiles are diverse (Table **1**). Based on their pharmacokinetic and pharmacodynamic properties, these insulins are characterized and administered [21].

Table 1. Different types of insulins.

Insulin Type	Examples	Onset of Action (min)	Time to Peak (hours)	Duration (hours)	Administration
Rapid-acting	Aspart Lispro Glulisine	10-20	0.5-1.5	3-5	0-15min before or just after meals
Short-acting	Regular human	30-45	2-4	4-8	15-30min before meals
Intermediate-acting	NPH	60-120	4-8	12-20	Once or twice daily
Long-acting	Detemir	60-120	6-10	16-24	Usually once daily
	Glargine	60-120	No pronounced peak	~24	
	Degludec	60-120	No pronounced peak	Up to 72	
premixed	70/30NPH/R	30-40	4-8	12-20	Usually twice daily, 0-30min before meals
	70/30 protamine-aspart/aspart	10-20			
Concentrated	U-300 glargine	60-120	No pronounced peak	Up to 72	Once daily
	U-500 human regular	30-45	6-12	12-24	Twice daily
	U-200 degludec	60-120	No pronounced peak	>24	Once daily

There are numerous drawbacks to conventional prandial and basal insulin preparations for insulin therapy. First, regular insulin is absorbed slowly by the subcutaneous tissue. After 30 to 60 minutes, the metabolic effect begins, and the highest concentration is reached after two to three hours of injection. As a result, people who take insulin regularly are more likely to experience postmeal hyperglycemia and late-postprandial hypoglycemia. Second, peak glucose is markedly reduced by the conventional basal insulin isophane (NPH). NPH is absorbed from subcutaneous tissue at varying rates [22]. Due to these pharmacodynamic limitations, users are more likely to experience hypoglycemia at night and elevated glucose levels before pre-breakfast. Insulin analogs based on a modified amino acid sequence from the human insulin molecule have been developed to address these issues.

CHAPTER 3

Nanomedicine for Insulin Delivery in Diabetes

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Abstract: Diabetes is one of the common diseases in the world and its treatment faces challenges. Insulin is the main therapeutic agent used in the treatment of diabetic patients. However, it has several side effects and during the day, patients may need several insulin injections, which is not pleasant for them. Therefore, a controlled and prolonged release system is required to decrease the injection frequency, improve the bioavailability of insulin, and enhance the compliance of patients. Nanoparticles (NPs) based drug delivery systems (DDSs) have been considered for insulin delivery. NPs can improve the permeability of insulin by opening the tight junctions between intestinal epithelial cells and can protect insulin from the action of enzymes existing in the gastrointestinal (GI) tract.

Keywords: Delivery, Diabetes, Insulin, Nanoparticle.

INTRODUCTION

Diabetes is of two types in which the body cannot produce insulin (type 1) or is not sensitive to insulin (type 2) and; consequently, the blood glucose level is not well controlled [1]. Diabetes is one of the biggest global health challenges of the 21st century, and there are many people living with this disease [2, 3]. Diabetes is mainly caused by environmental influences, immune system dysfunction, mental factors, and genetics, which result in either insulin resistance or insufficient insulin secretion [4].

As mentioned, diabetes is a result of the inefficiency of insulin to convert glucose into energy. When this process is disrupted, blood glucose can rise to a level that has health consequences. Insulin is the main therapeutic agent used in the treatment of patients with diabetes [5]. Insulin is a globular protein with a molecular weight of 5808 Daltons, containing two chains, A (21 residues) and B

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(30 residues) that are linked together by disulfide bonds (Fig. **1**) [6]. Insulin is produced by β cells of the pancreas. When there is too much glucose in the blood, insulin converts extra glucose into glycogen and stores it in the liver [7].

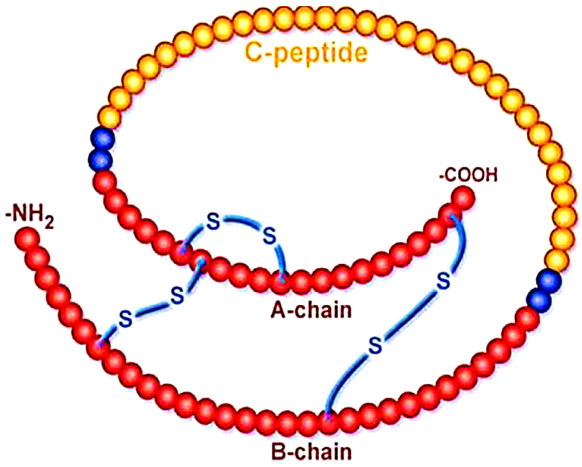

Fig. (1). Structure of insulin [8].

At present, the route of insulin administration is subcutaneous injection [9] which has several disadvantages including; lipohyperatrophy, obesity, retinopathy, hypoglycemia, neuropathy, lipoatrophy, allergic reactions and peripheral hyperinsulinemia [4, 10]. During the day, patients may need several insulin injections, which is not pleasant for most patients. Therefore, a controlled and prolonged release system is required to decrease the injection frequency and enhance the compliance of patients. According to the reports of Health Care Costs Institute, the cost of insulin for patients has doubled. Generally, oral delivery of peptide drugs is attractive due to patient compliance, patient adherence, and a cost-effective manufacturing process than injections. However, the gastrointestinal (GI) tract is a hostile milieu for the oral absorption of drugs due to low pH, existence of peptidases and proteases, and poor absorption through the intestinal epithelial layer. Furthermore, the hydrophilic nature of peptide drugs and the large molecular size further restrict their oral absorption [5, 11]. The bioavailability of insulin following oral delivery is usually lower than 1% owing to the enzymes existing in the GI tract and poor absorption *via* the intestinal epithelial cells [5].

Nanotechnology is a novel technology that will promote the next industrial revolution. Nanoparticles (NPs) based drug delivery systems (DDSs) have been considered to effectively transport various therapeutic agents to target cells. Nanocarriers are used for entrapment of drugs to limit their side effects and

improve their bioavailability. Organic and inorganic NPs have been employed for drug delivery. Various nanocarriers such as drug delivery system such as liposomes, polymeric NPs, solid lipid NPs (SLNs), chitosan, exosomes, micelles, nanogels and dendrimers have been widely investigated for encapsulation of insulin and increasing its bioavailability (Fig. **2**). The structure of some nanocarriers for insulin delivery is shown in Fig. (**3**). These nanocarriers are biodegradable, biocompatible, non-toxic and can escape from the reticuloendothelial system. Insulin encapsulated in NPs can be protected from the action of the enzymes existing in the GI tract. Moreover, NPs can improve the permeability of insulin to the intestinal mucosa through opening the tight junctions between intestinal epithelial cells [12]. In recent years, long-acting NPs formulations containing insulin have been developed to diminish the frequency of injections. Additionally, nanocarriers are widely considered for oral delivery of insulin [13]. Smart nanocarrier-based drug delivery systems were also developed for insulin delivery. For example, glucose-responsive NPs (synthesized from dextran) were prepared for rapid and extended self-regulated insulin delivery. Results showed that these formulations could reduce the elevated blood glucose levels in mice and decrease the risk of hypoglycemia [1]. Glucose-responsive self-assembled polyamines as smart NPs were also used for insulin delivery. These smart NPs could appropriately regulate blood glucose concentration [14].

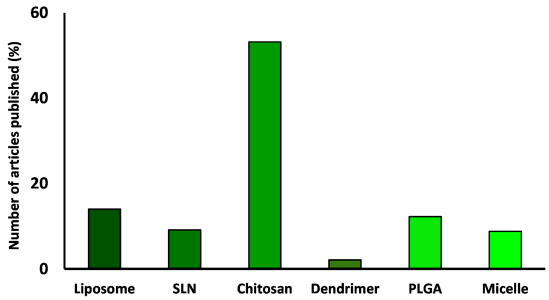

Fig. (2). Number of articles published in Elsevier, Springer, ACS, and Taylor & Francis journals from 2015 to 2022.

In oral insulin delivery, nanocarriers can improve the transport of insulin through the paracellular pathways. Chitosan can increase the paracellular transport of insulin through the interaction of positively charged polymers with the negatively charged cell membrane. Transcellular pathway is another mechanism for transporting insulin-loaded NPs. The transcellular pathway includes fusion, endocytosis, and adsorption. Moreover, receptor-mediated endocytosis is the major route for insulin-loaded nanocarriers to enter into cells [6, 15]. Fig. (**4**) illustrates the different delivery pathways of the insulin-loaded NPs.

CHAPTER 4

Nanoscience for Drug Delivery in Diabetes

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Abstract: Current conventional diabetes mellitus (DM) therapies are inadequate and have poor patient compliance. Subsequently, it is necessary to explore nanomedicine in managing diabetes. In recent years, several nanocarrier systems have been proven effective in various aspects of diabetes treatment, increasing drug stability, overcoming different biological barriers, and in enhancing bioavailability. Nanomedicine can potentially improve the therapeutic effect of drug substances to gain the patient's belief and impart a greater level of acceptability. In the present scientific spectrum, nanomedicines promise to provide sustained and targeted delivery with potential physical stability for a prolonged period, rendering a safe and effective therapy for diabetes. This chapter comprehensively elaborates on trends in the drug delivery system in treating diabetes for improved delivery of different classes of antidiabetic agents compared to contemporary therapies.

Keywords: Diabetes, Drug delivery, Inorganic nanocarriers, Nanomedicine, Organic nanocarriers, Targeting.

NANOMEDICINE IN DIABETES: NEED-BASED APPROACH

Diabetes mellitus constitutes clusters of metabolic disorders associated with higher blood glucose levels propelled by insulin resistance or deficiency [1]. Every year a substantial number of individuals are affected by this disorder. When the islet β-cell in the pancreas is significantly affected mostly by autoimmune destruction, it leads to Type–1 diabetes [2]. In other circumstances, insulin fails to trigger any response, and insulin resistance contributes to hyperglycemia [3]. Constant monitoring of glucose levels is significant to avoid any downstream impediment in the patients. Studies indicated that sustained hyperglycemia conditions would lead to macrovascular or microvascular complications [4].

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Traditionally diabetes patient is rigorously monitored for their glucose levels and subsequently administered insulin [5]. Patients are exhaustive with tedious and painful procedures leading to erratic glucose monitoring and meagre adherence. These patient factors precedent to irregular doses ultimately result in seizures and altered glucose levels [6]. There have been tremendous efforts made by researchers to develop continuous glucose monitors along with insulin pumps to tackle these patient difficulties. However, it is necessary to enhance these types of equipment for better management of diabetes. Over the years, there has been exponential growth in nanoscience that deliberated promising results for managing diabetes conditions [7]. Nanotechnology has delivered many breakthroughs explicitly in the medical field by enabling researchers to develop proficient nanosystems for delivering potential therapeutic molecules with enhanced benefits [8]. The principles of nanotechnology are exercised to design nanomedicines as nanotherapeutics; these systems enable the loading of the therapeutic moiety, subsequently enhancing its physiochemical properties, and achieving enhanced therapeutic benefits with precise targeting [9]. Nanotechnology has played a vital role in developing new-age glucose-monitoring devices. Fascinatingly, nanotechnology has potentiated the efforts of scientists in developing numerous delivery systems for improving insulin molecules and other antidiabetic molecules in the systemic circulation, surpassing the usual harsh metabolic pathway that deliberately reduces the efficacy of these molecules; thus, these nanosystems offer a better approach than conventional methods to deliver anti-diabetic molecules [10]. Diabetes is a very peculiar disease, especially type-2, *i.e*., severely affected by insulin resistance/deficiency. Interestingly, it was discovered that in a subcategory of type – 2, a significant number of patients experience varied blood–glucose levels due to obesity; these effects are independent of insulin. A certain number of patients suffer from insulin deficiency and other sections from insulin resistance [11]. These diabetic conditions have grabbed the attention of scientists, and it is believed that nanomedicine could play a potential role in managing these categories. In recent times, nanotechnological approaches have yielded new–age delivery systems capable of enhancing anti-diabetic molecules' potential [12]. Studies supported the vital role of various nano-formulations specially designed with novel smart polymers that successfully shield the drug molecules from harsh metabolic pathways; subsequently, these systems were instrumental in achieving a controlled release pattern of the loaded molecules, thus facilitating the maintained levels of insulin in patients [13]. The various transport mechanisms available for drug delivery of nanocarriers for the management of diabetes are illustrated in Fig. (**1**). Furthermore, constant monitoring of glucose levels is essential for diabetic patients. A more accurate, highly sensitive, robust nanosensors could be

deployed along with other nanomaterials in glucose monitoring devices which would drastically improve the patient's life [14].

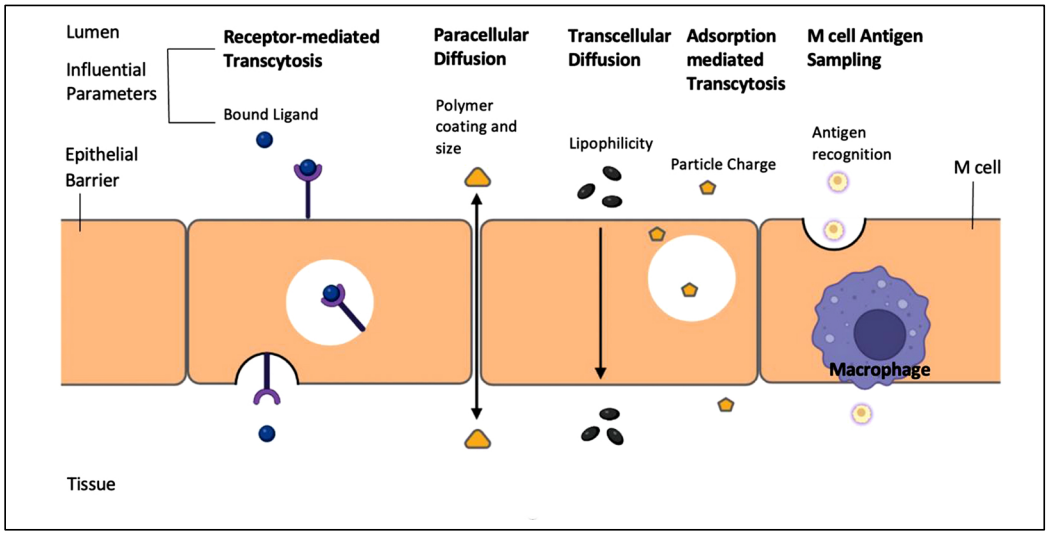

Fig. (1). Various transport mechanisms are available for drug delivery of nanocarriers for the management of diabetes.

Nanomedicine in the Management of Diabetes

Numerous types of nanomedicines have been studied as a drug delivery system for diabetes management as mentioned in Fig. (**2**).

ORGANIC MATERIAL-BASED NANOMEDICINES

Organic nanomaterials are nanocarriers assembled smartly from organic compounds and have drawn significant attention, notably for drug delivery in developing organic frameworks used in biomedical and pharmaceutical nanotechnology. Solid evidence of organic nanocarriers was investigated with lipid-based, natural, and synthetic polymeric nanocarriers.

Lipid-based Nanocarriers

Lipid-based nanocarriers are widely explored as carriers of drugs owing to their remarkable advantages due to their less toxicity, high loading efficiency, good stability, good protectivity, controlled and sustained release, affordable scale-up manufacturing, and targeted site-specific delivery through oral, topical, dermal, parenteral and pulmonary routes. The word lipid-based nanocarriers include liposomes, Solid Lipid Nanoparticles (SLNs), Nanostructured Lipid Carriers

CHAPTER 5

Nanoscience for Nucleotide Delivery in Diabetes

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Abstract: The convergence of nanoscience and nucleotide delivery holds tremendous promise in revolutionizing diabetes treatment. Nucleotide delivery emerged as a promising tool to modulate gene expression and cellular function in diabetes. Integration of nanoscience and nucleotide delivery in diabetes treatment opens avenues for efficient therapies. This approach has the potential to significantly improve glucose regulation and mitigate long-term complications associated with the disease. This chapter discussed DNA and RNA delivery approaches in diabetes treatment and the future and challenges of nucleotide delivery in diabetes.

Keywords: Delivery, Diabetes, Gene, Nanotechnology.

INTRODUCTION

Current treatments for diabetes often rely on insulin injections, oral medications, and lifestyle changes. However, gene therapy has emerged as a cutting-edge approach that has the potential to provide long-lasting solutions to this global health epidemic. Studies have shown that diabetes disease could be related to several genes [1, 2]. Furthermore, protein and small molecules delivery are limited and cannot be used for the treatment of every condition of disease. However, accordingly RNA and DNA are precursors of proteins, they can be used as a promising approach to the treatment of different diseases. Nucleotide delivery even can be used for gene editing of host's DNA to cure a genetic defect as opposed to just providing a simple treatment [3, 4]. Nucleotide delivery is defined as the delivery of genetic material including DNA plasmid, or RNA into the cell for production of desired proteins or inhibiting protein expression to correct or modulate a disease. Nucleic acids have a highly negative charge and their intracellular uptake is limited due to the presence of the force of repulsion between nucleic acids and the negatively charged plasma membrane. Furthermore, nucleic acids are rapidly cleared from the body due to degradation

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by endonucleases [5]. In this regard, studies have shown that cationic nanoparticles act as a powerful carrier for the protection of nucleic acids from degradation and also enhance the transfection efficiency and gene expression into the targeted tissue (Fig. **1**) [6].

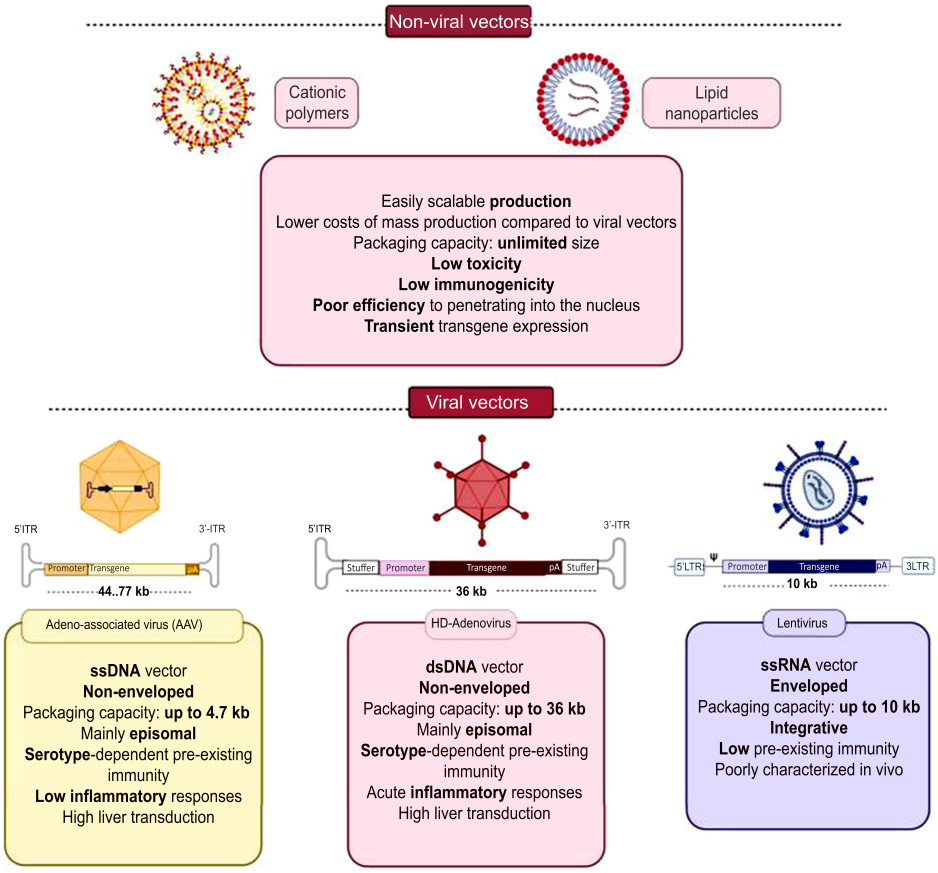

Fig. (1). Non-viral and viral vectors for nucleotide delivery [7].

Nanoscience has revolutionized the field of gene therapy, offering promising solutions to tackle complex diseases like diabetes. The integration of nanotechnology and gene therapy holds immense potential in transforming diabetes treatment [8].

The use of nanoparticles for nucleotide delivery could efficiently protect the degradation of nucleic acids and based on their chemical structure, increase nucleic acid cellular uptake and endosomal escape. In general, cationic

nanoparticles based on polymers or lipids will be used to electrostatically condense with the nucleic acid with negative charged [9]. The positive charge of nanoparticles is usually achieved by using amine groups in their structures which will be protonated at physiological pH (p*K*a ~7.4). Many studies investigated synthetic and natural polymers for nucleotide delivery, for example, chitosan, poly-L-lysine and polyethyleneimine [10, 11]. As mentioned in previous chapters, the use of conventional therapeutic agents and small molecule delivery for diabetes treatment and control of blood glucose has several limitations. Accordingly, newer physiological approaches like nucleotide delivery could be a good candidate for the treatment of diabetes. In this chapter, we briefly discussed DNA and RNA delivery by using nanoparticles for the treatment of different types of diabetes.

DNA DELIVERY APPROACH

Plasmid DNA can encode information for the expression of therapeutic proteins in different diseases. In one study, biodegradable poly [α-(4-aminobutyl)-L-glycolic acid] (PAGA) could efficiently protect plasmid DNA pCAGGS from degradation and reduce the development of insulitis in non-obese diabetic (NOD) mice. Their results have shown that using this polymeric nanoparticle could increase the stability of plasmid DNA from 10 minutes to 60 minutes and make serum mIL-10 level peak at 5 days which could be detectable for 9 weeks. The study showed that using PAGA/plasmid DNA complex could prevent autoimmune diabetes. This formulation significantly decreased severe insulitis in NOD mice, 15.7% insulitis in treated group compared with 90.9% in non-treated group [12]. In other study, researchers used cationic nanoparticles by blending lactide-co-glycolide (PLGA) and methacrylate copolymer (Eudragit® E100) to deliver a therapeutic DNA encoding mouse interleukin-10 in the muscle of mice. Their results have shown that the prepared nanoparticles could effectively escape from the endosome and the transfection efficiency was significantly higher than PLGA nanoparticles. Elevation of interleukin-10 level can facilitate the suppression of interferon-gamma levels, which can reduce islet infiltration. By muscular injection of cationic nanoparticles containing DNA plasmid IL-10, a lower blood glucose level was achieved compared with alone plasmid and histological assessment showed no chronic inflammatory responses in the muscles [13]. Studies demonstrated that muscular injection could be an efficient route for gene delivery due to good accessibility, and vascularization, which make it as a suitable route for gene delivery to make long-lasting protein expression [14 - 16].

As mentioned previously, glucagon-like peptide-1 (GLP-1) is a treatment option in diabetes. Researchers are trying to produce GLP-1 endogenously by using GLP-1 plasmid to diminish the injection of GLP-1 in diabetic patients as a

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Prof. Ali Rastegari is Assistant Professor of Pharmaceutical Nanotechnology in Iran University of Medical Sciences. He is recognized as an expert in nanotechnology for drug and gene delivery. He obtained his PharmD from Isfahan University of Medical Sciences, and Ph.D. in pharmaceutical nanotechnology from Tehran University of Medical Sciences. He worked for several months at Paris-Sud University and was interested in the development of nano based formulation for treatment of diseases, like diabetes mellitus.