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NANOPARTICLES APPLICATION AS A THERAPEUTIC STRATEGY FOR DIABETES MELLITUS MANAGEMENT

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The prevalence of diabetes, as reported by the World Health Organization and the International Diabetes Federation, has raised many eyebrows about the dangers of diabetes mellitus to society, leading to the development of various therapeutic techniques, including nanotechnological, in the management of this disease. This review discusses silver, gold, ceramic, alloy, magnetic, silica, polymeric nanoparticles and their various applications in diabetes management which may help to reduce the incidence of diabetes and its complication.

K e y w o r d s: nanoparticles and nanomaterials, diabetes mellitus, therapeutic applications.

Diabetes is a group of metabolic diseases in which a person has high blood sugar due to an inability to produce or metabolize enough insulin or an inability to metabolize glucose, which appears in the urine. Diabetes affects 171 million people (2.8% of the global population), according to the World Health Organization and the International Diabetes Federation. By 2030, this figure is expected to rise to 336 million (roughly 4.4 percent of the global population) [1].

Diabetes accounts for a significant portion of healthcare costs, as well as a high death rate, due to the high risk of organ malfunction and failure. Diabetes is linked to long-term complications (retinopathy, nephropathy, and peripheral neuropathy). All of these complications are caused by uncontrolled blood glucose levels (hyperglycemia) [1, 2]

The promotion of mitochondrial respiration, which results in the release of reactive oxygen species (ROS) into the cytoplasm, is one of the pathogenic pathways of these complications that are activated in diabetes due to hyperglycemia. The production of ROS causes oxidative stress, which leads to diabetic complications [3].

Diabetes mellitus was identified as the third leading cause of death in the United States, accounting for 13% of all deaths in 2010. Furthermore, pre-diabetes as a risk factor increases overall diabetes-related deaths by 2% [4]. Although this is a small increase, it reflects the greater risk of diabetes mellitus mortality. According to the International Diabetes Federation, nearly 415 million adults (aged 20–79 years) worldwide have diabetes mellitus [5]. This figure is expected to rise to 642 million [6] over the next 20 years.

Diabetes is "roughly" divided into two types: type 1 and type 2. Type 1 diabetes (T1DM) is distinguished by the inability of pancreatic β-cells to produce insulin, whereas type 2 diabetes (T2DM) is distinguished by reduced insulin production by the pancreas or insulin resistance in the tissues. T2DM is, in fact, a diverse disease. It was lately suggested that diabetic patients can be divided into five subgroups based on disease development and risk of diabetic complications [7]. These subgroups are: (a) severe autoimmune, (b) severe insulin-deficient, (c) severe insulin-resistant, (d) mild-obesity related, and (e) mild-age related diabetes.

A more comprehensive classification of diabetic patients could possibly prove an important step in the advancement of precision medicine in diabetes. Metformin (first-line treatment) is the most

commonly used pharmacological management of T2DM, followed by sulphonylureas, which can replace metformin as a first-line treatment but are most generally used as second-line treatment, and thiazolidinediones, which are a third-line therapy that can alternatively be used as second Newer treatments include incretin mimetics/analogs and dipeptidylpeptidase-4 (DPP-4) inhibitors that target the incretin axon (second-line treatment) [8] and sodium-glucose cotransporters inhibitors 2 (SGLT2) that target the reabsorption of glucose and can be used as monotherapy [9].

Nanomedicine is defined as "scientific and technological advancement at the nuclear, macromolecular, and molecular stages on the 1nm scale". Nanotechnology components have a size domain that is comparable to biological structures. A quantum dot, for example, is a small protein with a diameter of about 10 nm, as well as nanostructures that carry drugs and are 100 nm in size in certain viruses. Because of their similar size and functional properties, nanotechnology is a natural evolution in many areas of health-related studies, such as artificial and a prototype nanostructure that includes biological nanostructures like white cells and wound-healing particles, which detect and repair biological injuries and damages) [10].

Nanotechnology has become increasingly important in diabetic research over the last decade. This field encompasses nanomaterials, nanostructures, nanoparticle architecture, and human applications. It also provides more precise diabetes mellitus diagnosis information. Nanotechnology has improved drug delivery to areas that were previously inaccessible to macromolecules. It uses new implantable sensing technologies to provide accurate medical data.

Nanomedicine is a contemporary field that combines nanotechnology and medicine in order to improve human health care. Artificial pancreas, rather than pancreas replacement, artificial beta cells, oral insulin delivery using nanospheres as biodegradable polymeric reservoirs, and so on are some of the areas where nanotechnology can be used to effectively manage and treat diabetes mellitus [10]. This review discusses and addresses the use of nanotechnology in the effective treatment and management of diabetes.

Nanoparticles and nanomaterials

Nanoparticles (NPs) have a number of advantages over bulk structures because nano-materials are more dependent on shape and size, and interfaces are easier to access [11, 12]. Metallic nanoparticles (NPs), for example, exhibit distinct colors depending on their nano-size and shape, which can be used extensively in bioimaging applications [12, 13]. The application of nanomaterials and nanodevices in the field of health and medicine has paved the way for the development of a new nanoscience area, nanomedicine. One of the most significant contributions of nanotechnology to diabetes is the development of novel nano-sensors for simple, accurate, and sensitive blood glucose measurement [14]. Nanotechnology has enabled the development of robust insulin delivery vehicles that allow for the direct transfer of insulin molecules into the bloodstream, avoiding the acidic environment of the stomach and thus providing an alternative to daily injections [15]. Furthermore, nanotechnology is being used in the development of nanodrugs and bio-functional foods for the treatment of prediabetes [16].

The classification of type 2 diabetic patients into five subgroups highlights the disease's diversity, which is generally defined as a state of severe insulin deficiency or resistance. Indeed, the 5-subgroup classification reveals that T2DM is associated with obesity in more than 60% of patients, rather than insulin resistance or deficiency. Almost a quarter of the patients have insulin deficiency and 15% have insulin resistance [7].

Nanomedicine can be employed in the management of T2DM subgroups.

Specifically:

– *Drug delivery.* In the last few years, nanotechnology has found fruitful ground in the development of innovative deliveries that can potentially boost anti-diabetic regimes efficacy [17 ,18]. Various smart material formulations were developed with two main goals in mind: (a) protecting the drug by encapsulating it in a nano-carrier system and (b) efficiently releasing the drug in a steady as well manageable manner. Thus, antidiabetic regimens that promote insulin synthesis or reduce insulin release can be delivered to patients with insulin resistance and nano-formulations of insulin in individuals with insulin deficiency.

– *Diagnosis (detection and drug delivery).* Today, the treatment of diabetes is based on "open-loop" delivery methods. This means that the individual administers the drug to himself or herself at different times of day. "Closed-loop" therapy is the most advanced way to treat diabetes, in which the

individual has little to do to keep their blood sugar in check. As an example, a "synthetic pancreas", which is an external device that monitors glucose levels and pumps insulin, has been developed [19] that could be used to help people with Type 1 diabetes.

Nanosensors that are very sensitive and nanomaterials that help glucose sensors work better will eventually improve the lives of people who have diabetes (T1DM and T2DM).

Effect of nanoparticles on the occurrence of complications caused by diabetes

In recent years, the global prevalence of diabetes has climbed year by year, with a global prevalence rate of 9.3% in 2019. A great number of clinical studies have demonstrated that chronic hyperglycemia in the body can lead to a number of concomitant disorders. Diabetes can put a strain on the body's primary organs (cardiovascular, liver, kidney, and so on) and cause organ damage. Complications can be dangerous and may endanger patients' lives [20]. The following are the complications and the effect of nanoparticles on them:

Diabetic nephropathy. One of the most common causes of nephropathy is diabetic nephropathy (DN). At the moment, there is no efficient way to prevent the occurrence and progression of DN, and prevention and therapy of DN have yielded insufficient results. Over the last few years, nanotechnology has been incorporated to the treatment of DN, which can increase pharmacological efficacy and the prognosis of diabetic patients, effectively lowering pain and economic burden. The pathogenesis of DN is multifaceted, involving genetic factors being mutated; a dysfunction in glucose metabolism resulting in the activation of several endocrine pathways (the production of endothelial nitric oxide synthase (eNOS) and advanced glycation end products; and nitric oxide formation inhibition).

Yang X. [21] created and optimized the nanoformula of crocin-poly(lactic-co-glycolic acid-nanoparticle (CT-PLGA-NP), a therapeutic medication for streptozotocin-induced diabetic nephropathy. CT-PLGA-NPs demonstrated drug accumulation in the kidney and liver of diabetic rats, giving renal antifibrosis and anti-inflammatory actions. CT-PLGA-NP therapy reduced the synthesis and expression of renal fibrosis factors (TGF-1 and fibronectin) as well as inflammatory cytokines such as MCP-1 and TNF-α, as well as the activation of NF-B expression and PKC activity. Based on current research findings, we may conclude that CT-PLGA-NPs can alleviate diabetic nephropathy via antifibrosis and anti-inflammatory actions.

Ahangarpour A. et al. [22] investigated the effects of myricetin solid lipid nanoparticles (SLN) on streptozotocin-nicotinamide-induced DN in mice. Myricetin and its SLN administration reduced DN alterations by lowering oxidative stress and boosting antioxidant enzyme levels, with the latter effect being more pronounced in SLN-treated mice.

Ahad A. et al. [23] prepared nanoliposomes containing Eprosartan mesylate and tested them in STZ-induced diabetic nephropathy in Wistar rats; serum creatinine, urea, lactate dehydrogenase, total albumin, and malondialdehyde levels reduced significantly, indicating that Eprosartan mesylate-loaded nanoliposomes provided renal protection.

Diabetic retinopathy. Nanotechnology is widely employed in the treatment of diabetic retinopathy (DR) and has progressed to a new stage, where it is being used in clinical practice. With a rising number of diabetic patients, diabetic retinopathy (DR) has become the leading cause of blindness in those aged 16 to 64 [24]. Diabetes predisposing factors are quite complicated, including hypertension, hereditary factors, and so on. Pathological changes often refer to retinal edema, basement membrane thickening, microvascular obstruction, and blood-retinal barrier damage, all of which result in retinal edema and neovascularization [24, 25]. Researchers created silicate (SI) nanoparticles and investigated their antiangiogenesis properties on retinal neovascularization. Histological examination revealed that silicon nanoparticles had no toxicity to retinal tissue and could suppress the establishment of retinal neovascularization. As a result, silicon nanoparticles can effectively cure vascular endothelial growth factor-induced retinal neovascularization [26, 27].

Kim and colleagues published another work employing gold nanoparticle that demonstrated that gold nanoparticles impede retinal neovascularization. Gold nanoparticles substantially prevented the proliferation and migration of retinal microvascular endothelial cells, as well as the creation of a capillary-like network caused by vascular endothelial growth factor [26, 28]. Titanium dioxide (TiO2) nanoparticles are another type of nanoparticle reported by D. H. Jo et al. *In vitro*, it effectively inhibits angiogenesis and has no toxicity to the retina. Particles injected intravitreally also reduced neovascularzation. This study demonstrates that TiO2 nanopar-

ticles at the concentration level can be employed in the treatment of retinopathy animal models [26, 29].

Diabetic cardiomyopathy. Diabetic cardiomyopathy (DCM) is a myocardial condition that develops in diabetic persons and is not explained by other cardiac disorders. According to some research, oxidative stress injury to cardiac cells produced by diabetes mellitus is a major factor in the development of problems such as DCM [30]. The frequent clinical characteristics of DCM that contribute to future cardiac functional damage are myocardial fibrosis and apoptosis [31]. Another major pathogenic characteristic of DCM is microvascular disease. Diabetes mellitus causes myocardial microvascular dysfunction, which is linked to a reduction in left ventricular function [32].

In the nanoparticles employed in DCM, PSS-loaded nanoparticles were produced utilizing poly(lactic-co-glycolic acid) (PLGA) as a drug carrier and a modified double emulsion solvent evaporation process. Yu et al. investigated how PSS-NP affected vascular endothelial function in DCM rats. PSS-NP considerably improved ventricular wall motion and cardiac systolic and diastolic functioning in DCM rats. It has the ability to modulate the ultrastructure of cardiac microvascular endothelial cells in the DCM rat heart, hence reducing the progression of vascular endothelial dysfunction. Nitric oxide synthase (eNOS) and vascular endothelial growth factor A (VEGFA) concentrations in serum were considerably elevated, further reducing vascular endothelial damage in DCM rats [33].

Diabetic neuropathy. Diabetic peripheral neuropathy (DNP), a chronic condition that is a leading cause of foot ulceration and amputation, has a high prevalence rate of diabetic complications. According to relevant statistics [24, 34], DPN frequently develops alongside additional problems in many diabetes individuals. At this point in the clinical examination, it has been discovered that numerous factors, such as microvascular injury and glucose metabolism imbalance, are causing DPN. Simultaneously, immunological decline, vitamin and nerve growth factor deficiency, and the Schwann cell hypothesis are involved.

The activation of SGC is critical in the pathophysiology of DNP. The neuronal bodies in the dorsal root ganglion (DRG) are encapsulated by satellite glial cells (SGCs) . The purinergic 2 (P2) Y12 receptor was found on SGC in DRG. Curcumin is anti-inflammatory and anti-oxidant. Because curcumin has poor metabolic stability and bioavailability *in vivo*, encapsulated curcumin nanoparticles were utilized to increase targeting and bioavailability. Some researchers have conducted research on the two of them. Curcumin coated with nanoparticles can inhibit P2Y12 receptor expression on SGC in DRG and mechanical and thermal hyperalgesia in diabetic rats [35].

In DPN rats, nano-mir-146a-5p enhanced nerve conduction velocity and reduced morphological damage and demyelination of the sciatic nerve. In the sciatic nerve, nano-mir-146a-5p reduced the production of cytokines, caspase-3, and cleaved caspase-3. Mir-146a-5p nanoparticles can also stimulate the expression of myelin basic protein. These findings suggest that mir-146a-5p protects the peripheral nerve in the DPN rat model, possibly via modulating inflammatory responses and apoptosis [36].

Nanoparticles in the detection of insulin and blood sugar

Currently, blood glucose monitoring is intrusive and sometimes painful. As a result, the finger-prick test has been linked to diabetic patients' non-adherence to treatment regimens; however, it is also inaccurate and cannot be performed while doing other things. Because of its erratic nature, it can miss large and potentially dangerous spikes and changes in blood glucose levels during checks, such as while swimming or sleeping. Several improved approaches for non-invasive, continuous blood glucose monitoring have been proposed in recent years. Many of these benefit from nanotechnology's contributions to medical science [37].

A modern technique that uses nanotechnology to calculate minute insulin and blood sugar concentrations is a significant step toward assessing the health of the body's insulin-producing cells [37].

It can be achieved by the following ways:

– *Microphysiometer.* The microphysiometer is constructed from multi-walled carbon nanotubes, which are composed of multiple flat sheets of carbon atoms layered and rolled into very small tubes. Due to the superconductivity of the nanotubes, the volume of insulin in the chamber is proportional to the voltage at the electrode, and the nanotubes perform well at pH levels similar to those found in living cells. To determine insulin production, current detection methods collect small samples at regular intervals and calculate their insulin levels. The modern sensor monitors and senses insulin levels by

measuring the transfer of electrons produced as insulin molecules oxidize during glucose conversion [38].

The sensor's current increases as cells produce more insulin molecules, and vice versa, allowing real-time monitoring of insulin concentrations. This information could then be fed into an embedded microchip, which could wirelessly transmit the information to a wearable device [39].

– *Implantable sensor (Smart tattoo).* To measure diabetic blood sugar levels, polyethylene glycol beads filled with fluorescent molecules are implanted under the skin and remain in the interstitial fluid. The fluorescent molecules are displaced as sugar levels in the interstitial fluid fall to dangerously low levels, resulting in a glow. This light can be seen in a face tattoo.

Sensor microchips are now being developed to track vital body parameters in real time, such as pulse, temperature, and blood glucose. A chip would be implanted beneath the skin, emitting a signal that could be continuously tracked [40].

Therapeutic applications of nanoparticles in the management of diabetes

Zinc oxide nanoparticles (ZnONPs), a novel zinc delivery agent, have significant implications in the treatment of a wide range of diseases, including diabetes [41]. Preclinical studies have shown that zinc supplements have an ameliorative effect, so the development of zinc-based agents may be promising in the treatment of diabetes and its complications[42]. Some researchers investigated the anti-diabetic effects of ZnONPs by inducing insulin, insulin receptor, and glucose metabolizing enzyme gene expression [43]. In a similar vein, Umrani and Paknikar demonstrated the role of ZnONPs in blood glucose regulation in diabetic rats. In both studies, they only looked at the effect of ZnONPs on diabetic rats. In a recent study, ZnONPs were tested to confirm their anti-diabetic effect, and they used mouse models to measure their hypoglycemic and glucose tolerance effects because their effect had previously been studied in rat models [44].

Based on the data collected, ZnONPs showed promising anti-diabetic activity, implying that they could be used to develop an anti-diabetic drug. However, because the study did not investigate ZnONPs' physiological parameters or molecular mechanisms, more research is needed to support its anti-diabetic effects in mice [44].

Ceramic nanoparticles are composed of inorganic ceramic compounds such as titania, alumina, and silica [45]. These fragments provide a complete guide to the embedded molecules such as proteins, drugs to protect against the denaturing effects of temperature and external pH, and enzymes [46]. It has been revealed that hybrid nanospheres with cadmium-selenide quantum dots have active sensitivity and selectivity for tracking nitric oxide systems [47].

BioMEMS. Implantable Bio Micro Electro Mechanical Systems (BioMEMS) can be used as insulin pumps, distributing insulin in a holistic manner as blood sugar levels rise [48].

Another proposed BioMEMS device includes an insulin-filled drug delivery chamber. Biosensors and nonporous membranes with pores of 6 nm diameter are mounted on the outside to monitor increases in blood sugar levels and insulin secretion. The fabrication of a glucose-sensitive microvalve MEMS device for insulin administration is the focus of a review that delves into recent scientific efforts [49]. Another biocompatible polymer-based micropump device with embedded biosensors for optimal insulin delivery without consumer intervention was discovered in a recent study. Quantum computing technology has been improved to the nanoscale thanks to microfabrication strategies. Microneedles have also been reported to be effective transdermal insulin delivery systems [50].

Researchers previously described an integrated biocapsule with two microfabricated membranes merged together to form a cell-containing cavity bound by membranes with nanopores. Micromachined membranes with 18 nm pore sizes were generally thought to be permeable to tiny biomolecules such as oxygen, glucose, and insulin [51]. These biocapsules could be used to deliver insulin and treat diabetes in BioMEMS systems. The nanopores were designed to let glucose, insulin, and other metabolically active substances pass through, but they were too small to let larger cytotoxic cells, macrophages, antibodies, and complement pass through [51].

Gold nanoparticles. In addition, gold nanoparticles have been tested as insulin carriers. The ability of gold nanoparticles synthesized with chitosan as a reducing agent to transport insulin has been investigated [37]. The nanoparticles exhibited long-term aggregation stability and insulin loading of 53%.

In diabetic rats, chitosan acted as a reducing agent in the synthesis of gold nanoparticles while also promoting insulin penetration and absorption

through the oral and nasal mucosa. According to the findings, oral and nasal administration of insulin-loaded chitosan reduced gold nanoparticles while increasing insulin pharmacodynamic activity. Dextran nanoparticles combined with vitamin B_{12} have been shown to protect the gastrointestinal tract from the degradation of vitamin B_{12}-peptide/protein-drug abducts [52]. These nanoparticles were discovered to protect the entrapped insulin from gut proteases. Dextran nanoparticles and vitamin B_{12} release profiles were found to be suitable for oral insulin targeted delivery.

Diabetes is the root cause of a slew of other issues. Diabetes is linked to diabetic retinopathy (eyes), diabetic neuropathy (nervous system), cardiac disorders, kidney diseases, delayed wound healing, and other complications. The application of nanoparticulate systems to the treatment of these conditions has also been studied.

Over the last few decades, nanoparticle-based retinal drug delivery systems have been discovered [53]. Polyacrylic acid nanoparticles have advanced in their application in recent years.

Conclusion. The use of molecularly built materials and structures to track, repair, build, and govern human biological systems at the cellular level is known as nanotechnology. Using a microphysiometer and implantable sensors, it can monitor insulin and blood glucose levels. Nanoparticles were made utilizing nanotechnology, and these nanoparticles may aid in the treatment of diabetes. In which:

• Insulin is given to precise locations of action using polymeric nanoparticles;

• Insulin is administered orally. The use of polysaccharides and polymeric nanoparticles in oral insulin treatment is important for diabetes management because it eliminates the need for repeated subcutaneous injections.

Insulin is delivered by inhalable nanoparticles. Insulin molecules can be encased in nanoparticles and inhaled as a dry powder solution, making it appropriate for diabetes treatment. Its applications include the production of oral insulin, microspheres for the processing of oral insulin, an artificial pancreas, and nano pumps. The pump continuously distributes insulin to the patient's body, regulating the amount of sugar in his or her blood.

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ЗАСТОСУВАННЯ НАНОЧАСТИНОК ЯК ТЕРАПЕВТИЧНА СТРАТЕГІЯ У БОРОТЬБІ З ЦУКРОВИМ ДІАБЕТОМ

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Поширеність цукрового діабету за даними Всесвітньої організації охорони здоров'я та Міжнародної діабетичної федерації, спричинила сильне занепокоєння щодо небезпеки цукрового діабету для суспільства. Це призвело до розробки різних терапевтичних методів та підходів, у тому числі нанотехнологічних, для боротьби з цим захворюванням. У огляді розглянуто срібні, золоті, керамічні, сплавні, магнітні, кремнеземні, полімерні наночастинки та їх різноманітне застосування з метою зниження захворюваності на цукровий діабет та його ускладнень.

Ключові слова: наночастинки та наноматеріали, цукровий діабет, терапевтичне застосування.

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