A Review on nanoparticles as a promising approach to improving diabetes mellitus

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Abstract. Diabetes mellitus (DM) is a chronic disease condition that causes multiple complications in various organs such as kidney, reproductive system, and liver. It is mainly characterized by high blood glucose, insulin secretion deficiency or insulin resistance. In conventional diabetes, medications of insulin production and increased insulin sensitivity usually cause undesirable side effects and lead to poor adherence and therapy failure. In addition to insulin and oral hypoglycemic agents, there are different healthy ways to treat diabetes. Nanoparticles (NPs) such as zinc oxide (ZnO) NPs, selenium (Se) NPs, magnesium oxide (MgO) NPs, Copper (Cu) NPs, and cerium oxide (CeO2) NPs play an important role in controlling diabetes. The results reviewed here presented antidiabetic activity of CeO2 NPs, Se NPs, ZnO NPs, Cu NPs, and MgO NPs with fewer side effects when compared to antioxidant enzymes, glucose use, or increased insulin sensitivity, as these showed complications with diabetes.

1.Introduction

Diabetes mellitus (DM) is a medical problem characterized by hypoglycemia, when the affected individual cannot produce enough insulin, or the body cells are not respond to the glucose released by β-cells in the pancreas. According to the World Health report, diabetes is one of the most common causes of death in developing countries [1]. Hyperglycemia in diabetic patients causes three typical symptoms; polydipsia, polyuria, and polyphagia. DM is classified into three main types (i) Type1diabetes(T1D), (ii) type2diabetes(T2D), and (iii) gestational diabetes[2][3]. Diabetic patients undergo antidiabetic treatments that prevent hepatic gluconeogenesis and decrease insulin resistance, such as oral antidiabetic medicines. Therefore, using nanoparticles of trace elements for treating DM is considerable, such using copper, cerium, zinc, magnesium, and selenium-containing product[4–10]. Several previous studies demonstrated the role of trace minerals in glucose metabolism and their relationship to diabetes. Most of the complications of diabetes are due to oxidative stress, which leads to a decrease in the cellular content of zinc (Zn) enzymes and Zn-dependent antioxidants[4]. In this review, we explain the use of these nanoparticles to treat diabetes.

2.Review

2.1. Diabetes

Diabetes mellitus is one of the oldest illnesses that known to human beings. DM is a metabolic state generally characterized by high blood glucose levels, requiring daily monitoring and adequate supervision. Pancreatic beta cells generate the hormone insulin which enhances glucose uptake into cells to provide energy and also includes many other functions[3][5]. DM exists due to a lack of insulin synthesis or insulin sensitivity. It is mainly categorized into several classes but the most common forms are type1DM and type2 DM[2].

2.2. Clinical diagnosis

The diagnosis of diabetes is based on one of the four criteria of plasma glucose (PG): (i) a two-hour rise in PG during a 75-g oral glucose tolerance test (OGTT) (>200 mg/dL), an elevated fasting plasma glucose level (FPG) (>126 mg/dL), (iii) an elevated hemoglobin A1C level >6.5% or (iv) randomized elevation of PG (> 200 mg / dL) with classic hyperglycemic signs and symptoms. The American Diabetes Association (ADA) guidelines recommended that no diagnostic test be preferred over another [11][12].

2.3. Types of Diabetes

The DM is divided into three main forms. T1DM or insulin dependent diabetes mellitus (IDDM) accounts for 5–10 percent of all cases of diabetes and is caused by autoimmune defect of insulin-beta-cell in the pancreas. T2DM or non-insulin dependent DM (NIDDM) makes up 90-95 percent of diabetics and is affected by beta-cell loss combination and deficiency in target tissues along with IR[3]. Gestational diabetes appears to be another type of DM that occurs by definition in pregnant women and is primarily due to IR secondary to hormonal changes [13].

2.4. Insulin resistance

Insulin resistance is a disease disorder in which insulin dependent cells, such as adipocytes as well as skeletal muscles, do not respond adequately to normal insulin levels in the circulation. Since insulin plays a major role in introducing glucose into cells, any disturbance in insulin signal transduction is associated with hyperglycemia because of the cells' inability to absorb glucose. IR is a typical feature of most forms of metabolic disturbances, including obesity, hypertension, atherosclerosis, dyslipidemia, non-alcoholic fatty liver disease (NAFLD), metabolic syndrome, type 2 DM (T2DM), as well as some cases of T1D[14],[15].

2.5. Biological applications of nanoparticles for diabetes

Nanotechnology has emerged in the past few decades as a promising technique for many biomedical applications. Nanoparticles (NPs) are small materials with unique properties (at least < 100 nm in one of their dimensions). Reduction of materials to a nanoscale may also alter their properties, enabling them to interact in a specific way with cell biomolecules. Nanoparticles (NPs) for delivery to target cells are loaded with therapeutic agents[16]. Also, metal nanoparticles seem to be less harmful compared to mineral salts and have a multifunctional effect on the organism.[4].

2.5.1. Zinc oxide NPs

ZnO NPs are commonly used for a range of biomedical uses, including antidiabetic, antibacterial, anti-cancer, antifungal, drug delivery and anti-inflammatory activities[17]. Zinc is responsible for maintaining insulin structure [18] and plays a crucial role in insulin biosynthesis, secretion, and storage[19]. Research has shown that several zinc transporters, such as the zinc transporter-8, play a vital role in insulin secretion from pancreatic beta cells[5]. Zinc may also enhance insulin signaling by following various pathways, including increased insulin receptor phosphorylation, increased phosphoinositide 3-kinase activity, and glycogen synthase kinase-3 inhibition[5]. Also, changes in pancreatic tissue induced by diabetes can be restored by ZnO NPs [16]. Previous studies have tested ZnO NPs as well as a standard anti-diabetes drug to maintain cell function and structure in the t2d rat model and determine the efficiency of dipeptidyl peptidase-IV (DPP-IV) nanoparticles with or without zinc oxide using a Type 2 diabetes models. ZnO NPs

were synthesized with a total size of 20nm, using the sol-gel method. Ninety wistar rats were divided into three classes randomly after ten days of induction of diabetes. ZnONPs, as well as Vildagliptin, have been found to be positively active in the T2DM therapy [20]. The study by Nashwa et al., 2016 the therapeutic effects of ZnO NPs in reducing histological/functional changes in the pancreas of streptozotocin(STZ) - mediated rat model diabetes. Rats were randomized into groups of diabetes regulated, diabetic and ZnO NPs handled. ZnO NPs reversed pancreatic damage caused by diabetes, as shown by structural as well as ultrastructural changes and verified by mean a biochemical stability around blood sugar as well as serum insulin[16]. Another study reported by Kalakotla et al,2017 studied the antidiabetic activity of (Ag NPs), (CeO2 NPs), (ZnO NPs), and Momordica charantia (MC) on rats. The nanoparticles Ag NPs, CeO2 NPs, and ZnO NPs were synthesized by using the simple green synthesis style. It can be concluded that the ZnO NPs and Ag NPs had more effective anti-diabetic activity than MC and CeO2 NPs because of their broad pharmacological and biological properties [21]. A study by Govindasamy et al in 2017 on the synthesis of ZnO NPs using the reduction and capping potential of Andrographis paniculata leaf extract. The synthesized nanoparticles have been found to have strong biological activity with respect to antioxidants, anti-inflammatory, and anti-diabetes potentials that can be used in the cosmetics, food, and biomedical industries in various biological applications[22]. Another study by Abdolrahman et al in 2017 investigated the antidiabetic effects of thiamine and ZnO NPs after experimental DM. Fifty-six female mice have been used and divided into 7 groups of eight animals, and found that the thiamine has no negative impacts on pancreatic tissue. The treatment of diabetes was improved by ZnO nanoparticles alone or in combination with thiamine. In blood glucose as well as lipid parameters, this may indicate high levels of antidiabetic activity [23]. Research by Siamak et al,2017 tested whether ZnO NPs could be preventive against diabetes-related heart disease and compared it to ZnSO4.A total of 120 rats were classified as balanced and diabetic categories, randomly. ZnO NPs had dual benefits, as their mid-dose protects and cures heart damage. ZnSO4 also helped recover damage, but ZnO NPs' mid-dose was more effective than ZnSO4. In conclusion, ZnO NPs possess the ability to produce Zn in diabetic patients[24]. Abolfazl et al,2017 synthesized ZnO NPs in the presence of Vaccinium Arctostaphylos L, a fruit extract using a microwave-assisted process. The rats with alloxane-nduced diabetes were then divided into untreated rats (diabetic control group). In comparison with other treatment agents tested, ZnO NPs were found to be more effective in the treatment of alloxane-diabetic rats. [25]. Jihan et al,2018 investigated and compared the effect on insulin signaling pathways and insulin sensitivity of (AgNPs) and ZnO NPs in experimental diabetes. AgNPs and ZnONPs were prepared with pullulan (natural polymer) as a reduction. The results showed that Ag NPs and ZnO NPs were the best products relieving diabetes complications as well as insulin resistance. No major differentiation was found between the effect of ZnO NPs and Ag NPs in this research. [26]. Another previous study by Abolfazl et al in 2019 found that using Nasturtium officinale leaf extract would strongly stimulate ZnO nanoparticles to improve antidiabetic and enhance antibacterial activity [27]. Also, another study by Mohamed et al, investigated the impact of ZnO NPs in rats with streptozotocin-induced diabetes and its function in microRNA dysregulation. ZnO NP therapy resulted in marked improvements in blood insulin, glucose tolerance, and pancreatic cells function. The study found ZnO NPs to be a promising antidiabetic agent[28]. Moreover, a study by Shafayet et al., in 2020 prepared ZnO NPs by a sonochemical method. This study found that ZnONPs is a promising antidiabetic activity that can be used to develop an antidiabetic drug[5]. All previous studies demonstrated that ZnO NPs have a positive effect as a diabetes treatment and help reduce its complications.

2.5.2. Magnesium

Magnesium (Mg) is an important ion associated with the homeostasis of glucose. Also, Mg plays a major role in both phosphorylation and glucose metabolism by involving many enzymes involved in these reactions and may play a prominent role in insulin secretion.[4]. Mg deficiency resulted in insulin resistance, carbohydrate dyslipidemia, and complications of the DM mice. MgO NPs decreased blood sugar levels by improving insulin sensitivity as well as eliminating changes in lipid levelsuch as elevated LDL and triglyceride, and low HDL in diabetic mice [29]. A recent study by Kei et al, 2020 tested the polymer-directed aptamer (DPAP) system that was used as conductive transporters of MgO NPs coated for 3T3L1

diabetic target cell lines. MgO NPs were prepared by two methods; green biosynthesis strategies and sol-gel. 3,5-dinitrosalicylic acid (DNS) assay demonstrated the efficacy of DPAP-MgO NPs in delivering MgO NPs to target 3T3 L1 cells. As a result, sugar oxidation was reduced in 3T3 L1 cells, indicating that the treatment could be applied to t2d [8]. Through these studies, we conclude that magnesium can have an effective role in treating diabetes, especially type II diabetes, and this needs some other studies.

2.53. Cerium oxide NPs

There are many rare earth elements including Ce which are in the lanthanide series in the periodic table. CeO2 NPs have shown a promising new treatment for oxidative disorders that overcomes many previous brain injury therapies[30][31]. A study for the first time suggested that CeO2 NPs could be used as an effective therapeutic regenerative agent that prevents diabetes-induced nerve damage[30]. A previous study Rezvan et al,2017 investigated the neuroprotective effects of CeO2 nanoparticles in diabetic rats. Based on this study, we conclude that CeO2 nanoparticles can be used as an antioxidant to treat diabetic neuropathy[32]. Researches show that CeO2 NPs can help inhibit gestational diabetes complications and can be used as an antioxidant for treating diabetic neuropathy. However, further studies are needed.

2.5.4. Copper NPs

Copper is one of the most important transitional elements involved in many biochemical pathways. Cu NPs use effective trace metal NPs within the treatment of Type 2 diabetes, along with superior antioxidant properties and radical scraping in animals by inhibiting alpha-amylase and alpha-glucosidase [33]. Besides, Cu NPs showed substantial prevention of functional cardiovascular defects in diabetic. These NPs may increase nitric oxide bioavailability in the vascular endothelium and decrease oxidative stress [34]. Several previous studies have also shown that the use of copper nanoparticles plays an important role in the diagnosis of wounds in mice with diabetes not only can the illness be controlled by a strain of bacteria, but also can help in a faster healing [35][6]. In summary, there is a potential relationship between Cu NPs and diabetes patients.

2.5.5. Selenium NPs

Selenium is a trace element found in most plants. The body deficiency of selenium has been shown to cause various illnesses including diabetes [36]. The antioxidant properties of Se NPs are also less toxic than selenium itself. Se NPs have antioxidant effects by scavenging various peroxides, protecting lipids, and cellular macromolecules from oxidative damage to membranes, and by increasing glutathione peroxidase, and thioredoxine reductase levels. [37]. A research by Hanaa et al, 2016 on T2DM rats, showed that liposomal Se NPs have an antidiabetic capacity by maintaining beta-cell integrity, amplifying insulin secretion, reducing glucose levels, restoring the balance between oxidative and antioxidant production and reducing pancreatic inflammation[38]. Study by Mahnaz et al, 2017 indicated that at effective doses, selenium nanoparticles have beneficial effects on liver function and the treat associated disorders in rats by lowering blood sugar and by reducing levels of gamma-glutamyl transferase (GGT),aspartate aminotransferase (AST), alkaline phosphatase (ALP) ,alanine aminotransferase (ALT), [37]. Also in other studies, Se NPs displayed antidiabetic ability by preserving the integrity of pancreatic beta cells, reducing glucose levels, amplifying insulin and restoring the balance between oxidative and antioxidant output[39][7][40]. Se NPs is a promising treatment option that synergistically eliminates most complications of diabetes and insulin resistance.

3. Conclusion

The DM is an tremendous burden not only for patient's diabetes, but also for their families. All forms of diabetes should be identified as soon as possible, and treated properly to avoid its development and complications. The main reason diabetes treatment fails is non-compliance, primarily due to the unwanted side effects of traditional medicines. The latest discovery shows the potential for using nanoparticles as a

treatment for diabetes, it has used ZnO NPs, Cu NPs, Se NPs, CeO2 NPs, and MgO NPs that may have antidiabetic activity. It is also assumed to reduce the damage to the renal, pancreas, liver, and reproductive system caused by diabetes, by reducing oxidative stress and increase antioxidant, insulin sensitivity, and glucose utilization.

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